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       CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
       DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...'
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          1   FILE BIOTECHNO
          1   FILE CAPLUS
  21 FILES SEARCHED...
          2   FILE EMBASE
          1   FILE ESBIOBASE
  39 FILES SEARCHED...
          1   FILE MEDLINE
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  57 FILES SEARCHED...
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  78 FILES SEARCHED...
          1   FILE PATOSEP
         11   FILE PCTFULL
  91 FILES SEARCHED...

  11 FILES HAVE ONE OR MORE ANSWERS,   95 FILES SEARCHED IN STNINDEX

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FILE 'USPATFULL' ENTERED AT 18:10:23 ON 16 OCT 2002
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FILE 'PATOSEP' ENTERED AT 18:10:23 ON 16 OCT 2002

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L2 13 FILE USPATFULL
L3 11 FILE PCTFULL
L4 3 FILE EUROPATFULL
L5 2 FILE EMBASE
L6 1 FILE BIOSIS
L7 1 FILE BIOTECHNO
L8 1 FILE CAPLUS
L9 1 FILE ESBIOBASE
L10 1 FILE MEDLINE
L11 1 FILE SCISEARCH
L12 1 FILE PATOSEP

TOTAL FOR ALL FILES
L13 36 L1

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14 29 DUP REM L13 (7 DUPLICATES REMOVED)

=> d l14 1-29 ibib abs

L14 ANSWER 1 OF 29 USPATFULL
ACCESSION NUMBER: 2002:193026 USPATFULL
TITLE: METHOD FOR IDENTIFYING ALZHEIMER'S DISEASE THERAPEUTICS USING TRANSGENIC ANIMAL MODELS
INVENTOR(S): GAMES, KATE DORA, BELMONT, CA, UNITED STATES
SCHENK, DALE BERNARD, BURLINGAME, CA, UNITED STATES
MCCONLOGUE, LISA CLAIRE, SAN FRANCISCO, CA, UNITED STATES
SEUBERT, PETER ANDREW, SAN FRANCISCO, CA, UNITED STATES
RYDEL, RUSSELL E., BELMONT, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002104104	A1	20020801
APPLICATION INFO.:	US 1998-149718	A1	19980908 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-660487, filed on 7 Jun 1996, ABANDONED Continuation-in-part of Ser. No. US 1995-480653, filed on 7 Jun 1995, ABANDONED Continuation-in-part of Ser. No. US 1996-659797, filed on 7 Jun 1996, ABANDONED Continuation-in-part of Ser. No. US 1995-486538, filed on 7 Jun 1995, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS: 27

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Page(s)
LINE COUNT: 4514
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The construction of transgenic animal models of human Alzheimer's disease, and methods of using the models to screen potential Alzheimer's disease therapeutics, are described. The models are characterized by pathologies similar to pathologies observed in Alzheimer's disease, based on expression of all three forms of the .beta.-amyloid precursor protein (APP), APP695, APP751, and APP770, as well as various point mutations based on naturally occurring mutations, such as the London and Indiana familial Alzheimer's disease (FAD) mutations at amino acid 717, predicted mutations in the APP gene, and truncated forms of APP that contain the A.beta. region. Animal cells can be isolated from the transgenic animals or prepared using the same constructs with standard techniques such as lipofection or electroporation. The transgenic animals, or animal cells, are used to screen for compounds altering the pathological course of Alzheimer's disease as measured by their effect on the amount of APP, .beta.-amyloid peptide, and numerous other Alzheimer's disease markers in the animals, the neuropathology of the animals, as well as by behavioral alterations in the animals.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 2 OF 29 USPATFULL
ACCESSION NUMBER: 2002:78709 USPATFULL
TITLE: Method for treating inflammation
INVENTOR(S): Thompson, Penny, Snohomish, WA, UNITED STATES
Foster, Donald C., Lake Forest Park, WA, UNITED STATES
Xu, Wenfeng, Mukilteo, WA, UNITED STATES
Madden, Karen L., Bellevue, WA, UNITED STATES
Kelly, James D., Mercer Island, WA, UNITED STATES
Sprecher, Cindy A., Seattle, WA, UNITED STATES
Blumberg, Hal, Seattle, WA, UNITED STATES
Eagan, Maribeth A., Seattle, WA, UNITED STATES
Jaspers, Stephen R., Edmonds, WA, UNITED STATES
Chandrasekher, Yasmin A., Mercer Island, WA, UNITED STATES
Novak, Julia E., Bainbridge Island, WA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002042366	A1	20020411	
APPLICATION INFO.:	US 2000-746359	A1	20001222	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1999-171969P	19991223	(60)
	US 2000-213341P	20000622	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Paul G. Lunn, Esq., ZymoGenetics, Inc., 1201 Eastlake Avenue East, Seattle, WA, 98102
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 3393
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for treating IL-20 induced inflammation. An antagonist to IL-20 is administered to treat inflammation and associated diseases. The antagonist can be an antibody that binds to IL-20 or its receptor or a soluble receptor that binds to IL-20. Examples of such diseases are adult respiratory disease, psoriasis, eczema, contact dermatitis, atopic dermatitis, septic shock, multiple organ failure, inflammatory lung injury, bacterial pneumonia, inflammatory bowel disease, rheumatoid

arthritis, asthma, ulcerative colitis and Crohn's disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 3 OF 29 PCTFULL COPYRIGHT 2002 Univentio
ACCESSION NUMBER: 2002072607 PCTFULL ED 20020927 EW 200238
TITLE (ENGLISH): SOLUBLE HETERODIMERIC CYTOKINE RECEPTOR
TITLE (FRENCH): RECEPTEUR DE CYTOKINE HETERODIMERE SOLUBLE
INVENTOR(S): CHANDRASEKHER, Yasmin, A.; NOVAK, Julia, E.; FOSTER, Donald, C.; XU, Wenfeng; JASPERS, Stephen, R.
PATENT ASSIGNEE(S): ZYMOGENETICS, INC., for all designates States except US; CHANDRASEKHER, Yasmin, A., for US only; NOVAK, Julia, E., for US only; FOSTER, Donald, C., for US only; XU, Wenfeng, for US only; JASPERS, Stephen, R., for US only
AGENT: LUNN, Paul, G.
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002072607	A2	20020919

DESIGNATED STATES AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZM ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.:	WO 2002-US7214	A	20020307
PRIORITY INFO.:	US 2001-60/274,560		20010309
	US 2001-60/299,865		20010621

ABEN A soluble receptor that binds to IL-20 having two polypeptide subunits, IL-22R and IL-20RB. The two subunits are preferably linked together. In one embodiment one subunit is fused to the constant region of the light chain of an immunoglobulin, and the other subunit is fused to the constant region of the heavy chain of the immunoglobulin. The light chain and the heavy chain are connected via a disulfide bond.

ABFR L'invention concerne un recepteur soluble qui se fixe sur IL-20, comprenant deux sous-unites polypeptidiques, IL-22R et IL-22RB. Ces deux sous-unites sont de preferences liees. Dans un mode de realisation, une sous-unite est fusionnee avec la region constante de la chaine legere d'une immunoglobuline, et l'autre sous-unite est fusionnee avec la region constante de la chaine lourde de l'immunoglobuline. La chaine legere et la chaine lourde sont reliees par une liaison disulfure.

L14 ANSWER 4 OF 29 PCTFULL COPYRIGHT 2002 Univentio
ACCESSION NUMBER: 2002059377 PCTFULL ED 20020809 EW 200231
TITLE (ENGLISH): METHODS OF DIAGNOSIS OF BREAST CANCER, COMPOSITIONS AND METHODS OF SCREENING FOR MODULATORS OF BREAST CANCER
TITLE (FRENCH): PROCEDES DE DIAGNOSTIC DU CANCER DU SEIN, COMPOSITIONS ET PROCEDES DE CRIBLAGE DE MODULATEURS DU CANCER DU SEIN
INVENTOR(S): MACK, David, H.; GISH, Kurt, C.; AFAR, Daniel
PATENT ASSIGNEE(S): EOS BIOTECHNOLOGY, INC.
AGENT: BASTIAN, Kevin, L.
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE

WO 2002059377 A2 20020801

DESIGNATED STATES AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2002-US2242 A 20020124

PRIORITY INFO.: US 2001-60/263,965 20010124
US 2001-60/265,928 20010202
US 2001-09/829,472 20010409
US 2001-60/282,698 20010409
US 2001-60/288,590 20010504
US 2001-60/294,443 20010529

ABEN Described herein are genes whose expression are up-regulated or down-regulated in breast cancer. Related methods and compositions that can be used for diagnosis and treatment of breast cancer are disclosed. Also described herein are methods that can be used to identify modulators of breast cancer.

ABFR L'invention concerne des genes dont l'expression est regulee positivement ou negativement dans le cancer du sein. Elle concerne egalement des procedes et des compositions que l'on peut utiliser dans le diagnostic et le traitement du cancer du sein, ainsi que des procedes qui permettent d'identifier des modulateurs du cancer du sein.

L14 ANSWER 5 OF 29 PCTFULL

ACCESSION NUMBER: 2002057414 PCTFULL ED 20020801 EW 200230

TITLE (ENGLISH): LEUKOCYTE EXPRESSION PROFILING

TITLE (FRENCH): EVALUATION DU NIVEAU D'EXPRESSION LEUCOCYTAIRE

INVENTOR(S): WOHLGEMUTH, Jay; FRY, Kirk; MATCUK, George; ALTMAN, Peter; PRENTICE, James; PHILLIPS, Julie; LY, Ngoc; WOODWARD, Robert; QUERTERMOUS, Thomas; JOHNSON, Frances

PATENT ASSIGNEE(S): BIOCARDIA, INC., for all designates States except US; WOHLGEMUTH, Jay, for US only; FRY, Kirk, for US only; MATCUK, George, for US only; ALTMAN, Peter, for US only; PRENTICE, James, for US only; PHILLIPS, Julie, for US only; LY, Ngoc, for US only; WOODWARD, Robert, for US only; QUERTERMOUS, Thomas, for US only; JOHNSON, Frances, for US only

AGENT: WARD, Michael, R.

LANGUAGE OF FILING: English

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002057414	A2	20020725

DESIGNATED STATES AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-US47856 A 20011022

PRIORITY INFO.: US 2000-60/241,994 20001020
US 2001-60/296,764 20010608

ABEN Leukocyte gene expression profiling is utilized to identify oligonucleotides from gene expression candidate libraries. The expression libraries are generally immobilized on an array. Diagnostic oligonucleotide sets for analysis of leukocyte-related diseases are

described.

ABFR L'invention concerne l'evaluation du niveau d'expression genique d'un leucocyte utilise pour identifier des oligonucleotides a partir de bibliotheques candidates d'expression genique. Ces bibliotheques d'expression sont generalement immobilisees sur une matrice. L'invention concerne egalement un oligonucleotide de diagnostic regle de facon a analyser des maladies associees a un leucocyte.

L14 ANSWER 6 OF 29 EUROPATFULL COPYRIGHT 2002 WILA DUPLICATE 1

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

ACCESSION NUMBER: 1118681 EUROPATFULL EW 200130 FS OS
TITLE: METHOD FOR CONTROLLING THE RELEASE OF **GRANULES**
.
VERFAHREN ZUR KONTROLLIERTEN FREISETZUNG VON GRANULATEN.
PROCEDE DE COMMANDE DE LIBERATION DE **GRANULES**.
INVENTOR(S): SETO, Minoru, 572-33, Mitsuzawa, Fuji-shi, Sizuoka 417-0855, JP;
FUKUDA, Kouichirou, 282-1, Yunoki, Fuji-shi, Sizuoka 416-0908, JP
PATENT ASSIGNEE(S): Asahi Kasei Kabushiki Kaisha, 2-6, Dojimahama 1-chome, Kita-ku, Osaka-shi, Osaka 530-8205, JP
PATENT ASSIGNEE NO: 219576
AGENT: Forstmeyer, Dietmar, Dr. rer. nat., Dipl.-Chem. et al., Boeters & Bauer, Bereiteranger 15, 81541 Muenchen, DE
AGENT NUMBER: 77023
OTHER SOURCE: BEPA2001058 EP 1118681 A1 0021
SOURCE: Wila-EPZ-2001-H30-T1a
DOCUMENT TYPE: Patent
LANGUAGE: Anmeldung in Japanisch; Veroeffentlichung in Englisch; Verfahren in Englisch
DESIGNATED STATES: R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE
PATENT INFO.PUB.TYPE: EPA1 EUROPAEISCHE PATENTANMELDUNG (Internationale Anmeldung)
PATENT INFORMATION:

PATENT NO	KIND	DATE
EP 1118681	A1	20010725
'OFFENLEGUNGS' DATE:		20010725
APPLICATION INFO.:	EP 1999-944877	19990928
PRIORITY APPLN. INFO.:	JP 1998-274574	19980929
RELATED DOC. INFO.:	WO 99-JP5302	990928 INTAKZ
	WO 0018970	000406 INTPNR

L14 ANSWER 7 OF 29 USPATFULL
ACCESSION NUMBER: 2001:67794 USPATFULL
TITLE: Human respiratory syncytial virus peptides with antifusogenic and antiviral activities
INVENTOR(S): Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
PATENT ASSIGNEE(S): Trimeris, Inc., Durham, NC, United States (U.S. corporation)

NUMBER	KIND	DATE
PATENT INFORMATION: US 6228983	B1	20010508
APPLICATION INFO.: US 1995-485264		19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-470896, filed on 6 Jun 1995 Continuation-in-part of Ser. No. US 1994-360107, filed on 20 Dec 1994 Continuation-in-part of Ser. No. US 1994-255208, filed on 7 Jun 1994 Continuation-in-part of Ser. No. US 1993-73028, filed

on 7 Jun 1993, now patented, Pat. No. US 5464933

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Scheiner, Laurie
ASSISTANT EXAMINER: Parkin, Jeffrey S.
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 62
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 84 Drawing Figure(s); 83 Drawing Page(s)
LINE COUNT: 32166
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to peptides which exhibit antifusogenic and antiviral activities. The peptides of the invention consist of a 16 to 39 amino acid region of a human respiratory syncytial virus protein. These regions were identified through computer algorithms capable of recognizing the ALLMOTI5, 107x178x4, or PLZIP amino acid motifs. These motifs are associated with the antifusogenic and antiviral activities of the claimed peptides.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 8 OF 29 PCTFULL COPYRIGHT 2002 Univentio
ACCESSION NUMBER: 2001057190 PCTFULL ED 20020827
TITLE (ENGLISH): NOVEL NUCLEIC ACIDS AND POLYPEPTIDES
TITLE (FRENCH): ACIDES NUCLEIQUES ET POLYPEPTIDES
INVENTOR(S): TANG, Y., Tom; LIU, Chenghua; DRMANAC, Radoje, T.; ASUNDI, Vinod; ZHOU, Ping; XU, Chongjun; CAO, Yicheng; MA, Yunquing; ZHAO, Qing, A.; WANG, Dunrui; WANG, Jian-Rui; ZHANG, Jie; REN, Feiyan; CHEN, Rui-hong; WANG, Zhi, Wei; XUE, Aidong, J.; YANG, Yonghong; WEJHRMAN, Tom; GOODRICH, Ryle
PATENT ASSIGNEE(S): HYSEQ, INC.; TANG, Y., Tom; LIU, Chenghua; DRMANAC, Radoje, T.; ASUNDI, Vinod; ZHOU, Ping; XU, Chongjun; CAO, Yicheng; MA, Yunquing; ZHAO, Qing, A.; WANG, Dunrui; WANG, Jian-Rui; ZHANG, Jie; REN, Feiyan; CHEN, Rui-hong; WANG, Zhi, Wei; XUE, Aidong, J.; YANG, Yonghong; WEJHRMAN, Tom; GOODRICH, Ryle
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001057190	A2	20010809

DESIGNATED STATES: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.:	WO 2001-US4098	A	20010205
PRIORITY INFO.:	US 2000-09/496,914		20000203
	US 2000-09/560,875		20000427
	US 2000-09/598,075		20000620
	US 2000-09/620,325		20000719
	US 2000-09/654,936		20000901
	US 2000-09/663,561		20000915
	US 2000-09/693,325		20001020
	US 2000-09/728,422		20001130

ABEN The present invention provides novel nucleic acids, novel polypeptide sequences encoded by these nucleic acids and uses thereof.
ABFR L'invention concerne des acides nucleiques, des sequences polypeptidiques codees par ces acides nucleiques et leurs utilisations correspondantes.

L14 ANSWER 9 OF 29 PCTFULL COPYRIGHT 2002 Univentio
ACCESSION NUMBER: 2001011086 PCTFULL ED 20020828
TITLE (ENGLISH): NOVEL METHODS OF DIAGNOSIS OF ANGIOGENESIS, COMPOSITIONS AND METHODS OF SCREENING FOR ANGIOGENESIS MODULATORS
TITLE (FRENCH): NOUVELLES TECHNIQUES DE DIAGNOSTIC DE L'ANGIOGENESE, COMPOSITIONS ET TECHNIQUES DE CRIBLAGE POUR MODULATEURS D'ANGIOGENESE
INVENTOR(S): MURRAY, Richard
PATENT ASSIGNEE(S): EOS BIOTECHNOLOGY, INC.
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001011086	A2	20010215

DESIGNATED STATES AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2000-US22061 A 20000811
PRIORITY INFO.: US 1999-60/148,425 19990811
ABEN Described herein are methods that can be used for diagnosis of angiogenesis and angiogenic phenotypes. Also described herein are methods that can be used to screen candidate bioactive agents for the ability to modulate angiogenesis. Additionally, methods and molecular targets (genes and their products) for therapeutic intervention in disorders associated with angiogenesis are described.
ABFR

L14 ANSWER 10 OF 29 USPATFULL
ACCESSION NUMBER: 2000:105682 USPATFULL
TITLE: Human S100 proteins
INVENTOR(S): Hillman, Jennifer L., Mountain View, CA, United States
Bandman, Olga, Mountain View, CA, United States
Corley, Neil C., Mountain View, CA, United States
Lal, Preeti, Sunnyvale, CA, United States
Shah, Purvi, Sunnyvale, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

NUMBER	KIND	DATE
PATENT INFORMATION: US 6103497		20000815
APPLICATION INFO.: US 1998-205680		19981204 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1997-918727, filed on 21 Aug 1997, now patented, Pat. No. US 5849528
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kemmerer, Elizabeth
ASSISTANT EXAMINER: Romeo, David S.
LEGAL REPRESENTATIVE: Incyte Pharmaceuticals, Inc.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 2542
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides two human S100 proteins designated individually as S100P1 and S10OP2 and collectively as S100P, and polynucleotides which identify and encode S100P. The invention also provides expression vectors, host cells, agonists, antibodies and antagonists. The invention also provides methods for treating disorders associated with expression

of S100P.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 11 OF 29 USPATFULL
ACCESSION NUMBER: 2000:95093 USPATFULL
TITLE: Isolated peptides derived from the Epstein-Barr virus containing fusion inhibitory domains
INVENTOR(S): Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
PATENT ASSIGNEE(S): Trimeris, Inc., Durham, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6093794		20000725
APPLICATION INFO.:	US 1995-471913		19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-470896, filed on 6 Jun 1995 which is a continuation-in-part of Ser. No. US 1994-360107, filed on 20 Dec 1994 which is a continuation-in-part of Ser. No. US 1994-255208, filed on 7 Jun 1994 which is a continuation-in-part of Ser. No. US 1993-73028, filed on 7 Jun 1993, now patented, Pat. No. US 5464933
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Scheiner, Laurie
ASSISTANT EXAMINER: Parkin, Jeffrey S.
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 52 Drawing Figure(s); 83 Drawing Page(s)
LINE COUNT: 19949
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to peptides which exhibit potent anti-retroviral activity. The peptides of the invention comprise DP178 (SEQ ID:1) peptide corresponding to amino acids 638 to 673 of the HIV-1.sub.LAI gp41 protein, and fragments, analogs and homologs of DP178. The invention further relates to the uses of such peptides as inhibitory of human and non-human retroviral, especially HIV, transmission to uninfected cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 12 OF 29 USPATFULL
ACCESSION NUMBER: 2000:67564 USPATFULL
TITLE: Methods for inhibition of membrane fusion-associated events, including influenza virus
INVENTOR(S): Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
PATENT ASSIGNEE(S): Trimeris, Inc., Durham, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6068973		20000530
APPLICATION INFO.:	US 1995-485551		19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-470896, filed on 6 Jun 1995 which is a continuation-in-part of Ser. No. US 1994-360107, filed on 20 Dec 1994 which is a continuation-in-part of Ser. No. US 1994-255208, filed on 7 Jun 1994 which is a continuation-in-part of Ser. No. US 1993-73028, filed on 7 Jun 1993, now patented,

Pat. No. US 5464933
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Park, Hankyel
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 52 Drawing Figure(s); 83 Drawing Page(s)
LINE COUNT: 12021
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to peptides which exhibit potent anti-retroviral activity. The peptides of the invention comprise DP178 (SEQ ID:1) peptide corresponding to amino acids 638 to 673 of the HIV-1.sub.LAI gp41 protein, and fragments, analogs and homologs of DP178. The invention further relates to the uses of such peptides as inhibitory of human and non-human retroviral, especially HIV, transmission to uninfected cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 13 OF 29 USPATFULL
ACCESSION NUMBER: 2000:57361 USPATFULL
TITLE: Compositions for inhibition of membrane fusion-associated events, including influenza virus transmission
INVENTOR(S): Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
PATENT ASSIGNEE(S): Trimeris, Inc., Durham, NC, United States (U.S. corporation)
Duke University, Durham, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6060065		20000509
APPLICATION INFO.:	US 1995-475668		19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-470896, filed on 6 Jun 1995 which is a continuation-in-part of Ser. No. US 1994-360107, filed on 20 Dec 1994 which is a continuation-in-part of Ser. No. US 1994-255208, filed on 7 Jun 1994 which is a continuation-in-part of Ser. No. US 1993-73028, filed on 7 Jun 1993, now patented, Pat. No. US 5464933
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Achutamurthy, Ponnathapura
ASSISTANT EXAMINER: Parley, Hankyel T.
LEGAL REPRESENTATIVE: Pennie & Edmonds, LLP
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 84 Drawing Figure(s); 83 Drawing Page(s)
LINE COUNT: 19987
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to viral peptides referred to as "DP107- and DP178-like" peptides. Specifically, the invention relates to isolated influenza A DP107- and DP178-like peptides which are identified by sequence search motif algorithms. The peptides of the invention exhibit antiviral activity believed to result from inhibition of viral induced fusogenic events.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 14 OF 29 USPATFULL
ACCESSION NUMBER: 2000:50515 USPATFULL

TITLE: Screening assays for compounds that inhibit membrane fusion-associated events
INVENTOR(S): Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Jr., Stephen Robert, Cary, NC, United States
PATENT ASSIGNEE(S): Trimeris, Inc., Durham, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6054265		20000425
APPLICATION INFO.:	US 1997-919597		19970926 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-470896, filed on 6 Jun 1995 which is a continuation-in-part of Ser. No. US 1994-360107, filed on 20 Dec 1994 which is a continuation-in-part of Ser. No. US 1994-255208, filed on 7 Jun 1994 which is a continuation-in-part of Ser. No. US 1993-73028, filed on 7 Jun 1993, now patented, Pat. No. US 5464933
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Stucker, Jeffrey
LEGAL REPRESENTATIVE: Pennie & Edmonds, LLP
NUMBER OF CLAIMS: 1
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 83 Drawing Figure(s); 83 Drawing Page(s)
LINE COUNT: 21307
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to peptides which exhibit potent anti-retroviral activity. The peptides of the invention comprise DP178 (SEQ ID:1) peptide corresponding to amino acids 638 to 673 of the HIV-1.sub.LAI gp41 protein, and fragments, analogs and homologs of DP178. The invention further relates to the uses of such peptides as inhibitory of human and non-human retroviral, especially HIV, transmission to uninfected cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 15 OF 29 USPATFULL
ACCESSION NUMBER: 2000:12922 USPATFULL
TITLE: Isolated peptides derived from human immunodeficiency virus types 1 and 2 containing fusion inhibitory domains
INVENTOR(S): Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
PATENT ASSIGNEE(S): Trimeris, Inc., Durham, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6020459		20000201
APPLICATION INFO.:	US 1995-484223		19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-470896, filed on 6 Jun 1995 which is a continuation-in-part of Ser. No. US 1994-360107, filed on 20 Dec 1994 which is a continuation-in-part of Ser. No. US 1994-255208, filed on 7 Jun 1994 which is a continuation-in-part of Ser. No. US 1993-73028, filed on 7 Jun 1993, now patented, Pat. No. US 5464933
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Scheiner, Laurie
ASSISTANT EXAMINER: Parkin, Jeffrey S.
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP

NUMBER OF CLAIMS: 75
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 52 Drawing Figure(s); 83 Drawing Page(s)
LINE COUNT: 20335
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to peptides which exhibit potent anti-retroviral activity. The peptides of the invention comprise DP178 (SEQ ID:1) peptide corresponding to amino acids 638 to 673 of the HIV-1.sub.LAI gp41 protein, and fragments, analogs and homologs of DP178. The invention further relates to the uses of such peptides as inhibitory of human and non-human retroviral, especially HIV, transmission to uninfected cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 16 OF 29 USPATFULL
ACCESSION NUMBER: 2000:9527 USPATFULL
TITLE: Simian immunodeficiency virus peptides with antifusogenic and antiviral activities
INVENTOR(S): Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
Langlois, Alphonse J., Durham, NC, United States
PATENT ASSIGNEE(S): Trimeris, Inc., Durham, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6017536		20000125
APPLICATION INFO.:	US 1994-360107		19941220 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-255208, filed on 7 Jun 1994 which is a continuation-in-part of Ser. No. US 1993-73028, filed on 7 Jun 1993, now patented, Pat. No. US 5464933
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Scheiner, Laurie
ASSISTANT EXAMINER: Parkin, Jeffrey S.
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 50 Drawing Figure(s); 62 Drawing Page(s)
LINE COUNT: 20227
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to peptides which exhibit antifusogenic and antiviral activities. The peptides of the invention consist of a 16 to 39 amino acid region of a simian immunodeficiency virus (SIV) protein. These regions were identified through computer algorithms capable of recognizing the ALLMOTI5, 107.times.178.times.4, or PLZIP amino acid motifs. These motifs are associated with the antifusogenic and antiviral activities of the claimed peptides.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 17 OF 29 USPATFULL
ACCESSION NUMBER: 2000:4427 USPATFULL
TITLE: Measles virus peptides with antifusogenic and antiviral activities
INVENTOR(S): Barney, Shawn O'Lin, Cary, NC, United States
Lambert, Dennis Michael, Cary, NC, United States
Petteway, Stephen Robert, Cary, NC, United States
PATENT ASSIGNEE(S): Trimeris, Inc., Durham, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 6013263	20000111
APPLICATION INFO.:	US 1995-486099	19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-470896, filed on 6 Jun 1995 which is a continuation-in-part of Ser. No. US 1994-360107, filed on 20 Dec 1994 Ser. No. Ser. No. US 1994-255208, filed on 7 Jun 1994 And Ser. No. US 1993-73028, filed on 7 Jun 1993, now patented, Pat. No. US 5464933

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Scheiner, Laurie
ASSISTANT EXAMINER: Parkin, Jeffrey S.
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 52 Drawing Figure(s); 83 Drawing Page(s)
LINE COUNT: 19827
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to peptides which exhibit potent anti-retroviral activity. The peptides of the invention comprise DP178 (SEQ ID:1) peptide corresponding to amino acids 638 to 673 of the HIV-1.sub.LAI gp41 protein, and fragments, analogs and homologs of DP178. The invention further relates to the uses of such peptides as inhibitory of human and non-human retroviral, especially HIV, transmission to uninfected cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 18 OF 29 PCTFULL COPYRIGHT 2002 Univentio

ACCESSION NUMBER: 2000055629 PCTFULL ED 20020515
TITLE (ENGLISH): NOVEL METHODS OF DIAGNOSING AND TREATING BREAST CANCER, COMPOSITIONS, AND METHODS OF SCREENING FOR BREAST CANCER MODULATORS
TITLE (FRENCH): NOUVELLES TECHNIQUES PERMETTANT DE TRAITER ET DE DIAGNOSTIQUER LE CANCER DU SEIN, COMPOSITIONS ET TECHNIQUES DE CRIBLAGE POUR MODULATEURS DE CANCER DU SEIN
INVENTOR(S): MACK, David; GISH, Kurt, C.
PATENT ASSIGNEE(S): EOS BIOTECHNOLOGY, INC.; MACK, David; GISH, Kurt, C.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2000055629	A2	20000921
DESIGNATED STATES	AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 2000-US6952	A	20000315
PRIORITY INFO.:	US 1999-09/268,865		19990315
	US 1999-09/439,878		19991112
	US 1999-09/440,370		19991112
	US 1999-09/440,493		19991115
	US 1999-09/440,676		19991116
	US 1999-09/440,677		19991116
	US 1999-09/450,810		19991129
	US 1999-09/453,137		19991202
	US 2000-09/453,137		20000308

ABEN Described herein are methods that can be used for diagnosis and

prognosis of breast cancer.
Also described herein are methods that can be used to screen candidate bioactive agents for the
ability to modulate breast cancer. Additionally, methods and molecular targets (genes and their
products) for therapeutic intervention in breast and other cancers are described.

ABFR L'invention concerne des techniques utilisees pour diagnostiquer et pronostiquer le cancer du
sein. L'invention concerne egalement des techniques pouvant etre utilisees pour cribler des agents
bioactifs candidats, permettant de moduler le cancer du sein. L'invention concerne, en outre, des
techniques et des cibles moleculaires (genes et leurs produits) permettant d'intervenir
therapeutiquement dans le cancer du sein et dans d'autres cancers.

L14 ANSWER 19 OF 29 PCTFULL COPYRIGHT 2002 Univentio

ACCESSION NUMBER: 2000052204 PCTFULL ED 20020515
TITLE (ENGLISH): GENE EXPRESSION IN BLADDER TUMORS
TITLE (FRENCH): EXPRESSION GENIQUE DANS LES TUMEURS DE LA VESSIE
INVENTOR(S): ORNTOFT, Torben, F.
PATENT ASSIGNEE(S): ORNTOFT, Torben, F.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2000052204	A2	20000908

DESIGNATED STATES: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.:	WO 2000-IB367	A	20000222
PRIORITY INFO.:	US 1999-60/121,124		19990222

ABEN Methods for analyzing tumor cells, particularly bladder tumor cells employ gene expression
analysis of samples. Gene expression patterns are formed and compared to reference patterns.
Alternatively gene expression patterns are manipulated to exclude genes which are expressed in
contaminating cell populations. Another alternative employs subtraction of the expression of genes
which are expressed in contaminating cell types. These methods provide improved accuracy as well as
alternative basis for analysis from diagnostic an prognostic tools currently available.

ABFR L'invention concerne des procedes d'analyse des cellules cancereuses, particulierement des
cellules cancereuses de la vessie recourant a l'analyse genique d'echantillons. Les modeles
d'expression genique sont formes et compares a des modeles de reference. Selon une variante, les
modeles d'expression genique sont manipules pour exclure les genes qui sont exprimes dans des
populations de cellules contaminantes. Selon une autre variante, on utilise la soustraction de
l'expression des genes qui sont exprimes dans des types de cellules contaminantes. Ces procedes
assurent une plus grande precision et servent de base pour l'analyse a partir d'outils de diagnostic

et de pronostic disponibles sur le marche.

L14 ANSWER 20 OF 29 EUROPATFULL COPYRIGHT 2002 WILA

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

ACCESSION NUMBER: 1059354 EUROPATFULL EW 200050 FS OS
TITLE: Sequence-determined DNA fragments and corresponding polypeptides encoded thereby.
DNS-fragmente mit bestimmter Sequenz und die dadurch kodierte Polypeptide.
Fragments d'ADN avec des sequences determinees et polypeptides encodees par lesdits fragments.
INVENTOR(S): Alexandrov, Nickolai, 1404 Oak Trail St., Thousand Oaks, CA 91320, US;
Troukhan, Maxim E., 1675 Amberwood Dr. No. 2, South Pasadena, CA 91030, US
PATENT ASSIGNEE(S): Ceres Incorporated, 3007 Malibu Canyon Road, Malibu, CA 90265, US
PATENT ASSIGNEE NO: 2967260
AGENT: Bannerman, David Gardner et al., Withers & Rogers, Goldings House, 2 Hays Lane, London SE1 2HW, GB
AGENT NUMBER: 28001
OTHER SOURCE: BEPA2000096 EP 1059354 A2 0418
SOURCE: Wila-EPZ-2000-H50-T1a
DOCUMENT TYPE: Patent
LANGUAGE: Anmeldung in Englisch; Veroeffentlichung in Englisch
DESIGNATED STATES: R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE; R AL; R LT; R LV; R MK; R RO; R SI
PATENT INFO.PUB.TYPE: EPA2 EUROPAEISCHE PATENTANMELDUNG
PATENT INFORMATION:

PATENT NO	KIND	DATE
EP 1059354	A2	20001213
'OFFENLEGUNGS' DATE:		20001213
APPLICATION INFO.:	EP 2000-304943	20000612
PRIORITY APPLN. INFO.:	US 1999-138540	19990610
	US 1999-138847	19990610

L14 ANSWER 21 OF 29 EUROPATFULL COPYRIGHT 2002 WILA

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

ACCESSION NUMBER: 1033405 EUROPATFULL EW 200036 FS OS
TITLE: Sequence-determined DNA fragments and corresponding polypeptides encoded thereby.
DNS-fragmente mit bestimmter Sequenz und die dadurch kodierte Polypeptide.
Fragments d'ADN avec des sequences determinees et polypeptides encodees par lesdits fragments.
INVENTOR(S): Alexandrov, Nickolai, 1404 Oak Trail St., Thousand Oaks, CA 91320, US;
Brover, Vyacheslav, 5916 N. Las Virgenes Rd. #590, Calabasas, CA 91302, US;
Chen, Xianfeng, 1705 S. Westgate Ave. #2, Los Angeles, CA 90025, US;
Subramanian, Gopalakrishnan, 4205 Peach Slope Rd., Moorpark, CA 93021, US;
Troukhan, Maxim E., 1675 Amberwood Dr. #2, South Pasadena, CA 91030, US;
Zheng, Liansheng, 12333 Wild Turkey Court, #B, Creve Coeur, MO 63141, US;
Dumas, J., US
PATENT ASSIGNEE(S): Ceres Incorporated, 3007 Malibu Canyon Road, Malibu, CA

	90265, US
PATENT ASSIGNEE NO:	2967260
AGENT:	Bannerman, David Gardner et al., Withers & Rogers, Goldings House, 2 Hays Lane, London SE1 2HW, GB
AGENT NUMBER:	28001
OTHER SOURCE:	BEPA2000068 EP 1033405 A2 0344
SOURCE:	Wila-EPZ-2000-H36-T1a
DOCUMENT TYPE:	Patent
LANGUAGE:	Anmeldung in Englisch; Veroeffentlichung in Englisch
DESIGNATED STATES:	R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE; R AL; R LT; R LV; R MK; R RO; R SI
PATENT INFO.PUB.TYPE:	EPA2 EUROPAEISCHE PATENTANMELDUNG
PATENT INFORMATION:	

PATENT NO	KIND	DATE
EP 1033405	A2	20000906
'OFFENLEGUNGS' DATE:		20000906
APPLICATION INFO.:	EP 2000-301439	20000225
PRIORITY APPLN. INFO.:	US 1999-121825	19990225
	US 1999-123180	19990305
	US 1999-123548	19990309
	US 1999-125788	19990323
	US 1999-126264	19990325
	US 1999-126785	19990329
	US 1999-127462	19990401
	US 1999-128234	19990406
	US 1999-128714	19990408
	US 1999-129845	19990416
	US 1999-130077	19990419
	US 1999-130449	19990421
	US 1999-130891	19990423
	US 1999-130510	19990423
	US 1999-131449	19990428
	US 1999-132407	19990430
	US 1999-132048	19990430
	US 1999-132484	19990504
	US 1999-132485	19990505
	US 1999-132487	19990506
	US 1999-132486	19990506
	US 1999-132863	19990507
	US 2000-176866	20000119
	US 2000-176867	20000119
	US 2000-176910	20000119
	US 2000-178166	20000126
	US 2000-178545	20000127
	US 2000-178547	20000127
	US 2000-177666	20000127
	US 2000-178546	20000127
	US 2000-178544	20000127
	US 2000-178754	20000128
	US 2000-178755	20000128
	US 2000-179388	20000201
	US 2000-179395	20000201
	US 2000-180139	20000203
	US 2000-180039	20000203
	US 2000-180206	20000204
	US 2000-180207	20000204
	US 2000-180696	20000207
	US 2000-180695	20000207
	US 2000-181214	20000209
	US 2000-181228	20000209
	US 2000-181551	20000210
	US 2000-181476	20000210
	US 2000-182478	20000215

	US 2000-182477	20000215
	US 2000-182516	20000215
	US 2000-182512	20000215
	US 2000-183166	20000217
	US 2000-183165	20000217

L14 ANSWER 22 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 2000080321 EMBASE
TITLE: Calcium-dependent **secretion** in human neutrophils: A proteomic approach.
AUTHOR: Boussac M.; Garin J.
CORPORATE SOURCE: Dr. M. Boussac, CEA/Grenoble, Dept. Biol. Moleculaire/Structurale, Laboratoire de Chimie des Proteines, 17, rue des Martyrs, F-38054 Grenoble Cedex 9, France. muriel.boussac@cea.fr
SOURCE: Electrophoresis, (2000) 21/3 (665-672).
Refs: 43
ISSN: 0173-0835 CODEN: ELCTDN
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Bactericidal, proteolytic and signal proteins released by activated neutrophils play a major role in infection fighting and inflammatory processes. These proteins are mainly stored in organelles called **granules** until induction of their controlled exocytosis. The present work deals with the characterization of the proteins which are secreted upon activation of human neutrophils by ionomycin and calcium. Proteins were separated by two- dimensional gel electrophoresis and identified by peptide mass fingerprinting. Almost all the previously described soluble components of neutrophil **granules** could be identified. Moreover, several additional proteins were shown to be secreted by activated neutrophils, namely **calgranulins**, human cartilage glycoprotein of 39 kDa (HC gp-39), chitotriosidase, and annexin XI. Their subcellular localization and possible functions are discussed.

L14 ANSWER 23 OF 29 PCTFULL COPYRIGHT 2002 Univentio
ACCESSION NUMBER: 1999051766 PCTFULL ED 20020515
TITLE (ENGLISH): METHODS FOR PRODUCING LIBRARIES OF EXPRESSIBLE GENE SEQUENCES
TITLE (FRENCH): METHODES DE PRODUCTION DE BANQUES DE SEQUENCES DE GENES EXPRIMABLES
INVENTOR(S): FERNANDEZ, Joseph, Manuel; HEYMAN, John, Alastair; HOEFFLER, James, Paul; MARKS-HULL, Heather, Lynn; SINDICI, Michelle, Lynn
PATENT ASSIGNEE(S): INVITROGEN; FERNANDEZ, Joseph, Manuel; HEYMAN, John, Alastair; HOEFFLER, James, Paul; MARKS-HULL, Heather, Lynn; SINDICI, Michelle, Lynn
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9951766	A1	19991014
DESIGNATED STATES	AU CA JP US AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	WO 1999-US7270	A	19990402
PRIORITY INFO.:	US 1998-09/054,936		19980403

ABEN The present invention comprises a method for producing libraries of expressible gene sequences.
The method of the invention allows for the simultaneous manipulation of multiple gene sequences and
thus allows libraries to be created in an efficient and high throughput manner. The expression

vectors containing verified gene sequences can be used to transfect cells for the production of
recombinant proteins. The invention further comprises libraries of expressible gene sequences
produced using the method of the invention and expression vectors used in the construction of said
libraries.

ABFR La presente invention concerne une methode de production de banques de sequences de genes
exprimables. La methode selon l'invention permet la manipulation simultanee de plusieurs sequences
de genes et permet donc de creer des banques de maniere efficace et a un debit eleve. On peut
utiliser les vecteurs d'expression afin de produire des proteines de recombinaison. L'invention
concerne en outre des banques de sequences de genes exprimables produites grace a la methode selon
l'invention et des vecteurs d'expression utilises dans l'elaboration de ces banques.

L14 ANSWER 24 OF 29 PCTFULL COPYRIGHT 2002 Univentio

ACCESSION NUMBER:	1999051620 PCTFULL ED 20020515
TITLE (ENGLISH):	LIBRARIES OF EXPRESSIBLE GENE SEQUENCES
TITLE (FRENCH):	BANQUES DE SEQUENCES DE GENES POUVANT ETRE EXPRIMEES
INVENTOR(S):	FERNANDEZ, Joseph, Manuel; HEYMAN, John, Alastair; HOEFFLER, James, Paul
PATENT ASSIGNEE(S):	INVITROGEN
LANGUAGE OF PUBL.:	English
DOCUMENT TYPE:	Patent
PATENT INFORMATION:	

NUMBER	KIND	DATE
WO 9951620	A1	19991014

DESIGNATED STATES	AU CA JP AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.:	WO 1999-US7334 A 19990402
PRIORITY INFO.:	US 1998-60/080,626 19980403
	US 1998-60/096,981 19980818

ABEN The invention described herein comprises libraries of expressible gene sequences. Such gene
sequences are contained on plasmid vectors designed to endow the expressed proteins with a number of
useful features such as affinity purification tags, epitope tags, and the like. The expression
vectors containing such gene sequences can be used to transfect cells for the production of
recombinant proteins. A further aspect of the invention comprises methods of identifying binding
partners for the products of such expressible gene sequences.

ABFR L'invention concerne des banques de sequences de genes pouvant etre exprimees. Ces sequences de
genes sont contenues dans des vecteurs plasmidiques concus pour conferer aux proteines exprimees
certaines caracteristiques utiles telles que celles de marqueurs de purification par affinite, de
marqueurs d'epitope et analogue. Les vecteurs d'expression contenant ces sequences de genes peuvent
etre utilises pour transfecter des cellules en vue de la production de proteines recombinees. Un
autre aspect de l'invention concerne des procedes d'identification de partenaires de liaison pour
les produits de ces sequences de genes pouvant etre exprimees.

L14 ANSWER 25 OF 29 PCTFULL COPYRIGHT 2002 Univentio

ACCESSION NUMBER:	1999038972 PCTFULL ED 20020515

TITLE (ENGLISH): HUMAN GENES AND GENE EXPRESSION PRODUCTS II
TITLE (FRENCH): GENES HUMAINS ET PRODUITS II D'EXPRESSION GENIQUE
INVENTOR(S): WILLIAMS, Lewis, T.; ESCOBEDO, Jaime; INNIS, Michael, A.; GARCIA, Pablo, Dominguez; SUDDUTH-KLINGER, Julie; REINHARD, Christoph; GIESE, Klaus; RANDAZZO, Filippo; KENNEDY, Giulia, C.; POT, David; KASSAM, Altaf; LAMSON, George; DRMANAC, Radoje; CRKVENJAKOV, Radomir; DICKSON, Mark; DRMANAC, Snezana; LABAT, Ivan; LESHKOWITZ, Dena; KITA, David; GARCIA, Veronica; JONES, Lee, William; STACHE-CRAIN, Birgit
PATENT ASSIGNEE(S): CHIRON CORPORATION; HYSEQ INC.; WILLIAMS, Lewis, T.; ESCOBEDO, Jaime; INNIS, Michael, A.; GARCIA, Pablo, Dominguez; SUDDUTH-KLINGER, Julie; REINHARD, Christoph; GIESE, Klaus; RANDAZZO, Filippo; KENNEDY, Giulia, C.; POT, David; KASSAM, Altaf; LAMSON, George; DRMANAC, Radoje; CRKVENJAKOV, Radomir; DICKSON, Mark; DRMANAC, Snezana; LABAT, Ivan; LESHKOWITZ, Dena; KITA, David; GARCIA, Veronica; JONES, Lee, William; STACHE-CRAIN, Birgit
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9938972	A2	19990805
DESIGNATED STATES	AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG		
APPLICATION INFO.:	WO 1999-US1619	A	19990128
PRIORITY INFO.:	US 1998-60/072,910		19980128
	US 1998-60/075,954		19980224
	US 1998-60/080,114		19980331
	US 1998-60/080,515		19980403
	US 1998-60/080,666		19980403

ABEN This invention relates to novel human polynucleotides and variants thereof, their encoded polypeptides and variants thereof, to genes corresponding to these polynucleotides and to proteins expressed by the genes. The invention also relates to diagnostic and therapeutic agents employing such novel human polynucleotides, their corresponding genes or gene products, e.g., these genes and proteins, including probes, antisense constructs, and antibodies.

ABFR Cette invention concerne des nouveaux polynucleotides humains et des variants de ceux-ci, des polypeptides codes de ceux-ci et leurs variants, des genes correspondant a ces polynucleotides ainsi que des proteines exprimees par ces genes. L'invention concerne egalement des agents diagnostiques et therapeutiques mettant en oeuvre ces nouveaux polynucleotides humains, les genes ou produits geniques correspondants de ceux-ci, par exemple ces genes et proteines, y compris des sondes, des constructions anti-sens ainsi que des anticorps.

L14 ANSWER 26 OF 29 USPATFULL
ACCESSION NUMBER: 1998:157140 USPATFULL
TITLE: Polynucleotides encoding a human S100 protein
INVENTOR(S): Hillman, Jennifer L., Mountain View, CA, United States
Bandman, Olga, Mountain View, CA, United States
Corley, Neil C., Mountain View, CA, United States

Lal, Preeti, Sunnyvale, CA, United States
Shah, Purvi, Sunnyvale, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc.., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5849528		19981215	
APPLICATION INFO.:	US 1997-918727		19970821	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Spector, Lorraine
ASSISTANT EXAMINER: Romeo, David S.
LEGAL REPRESENTATIVE: Incyte Phamaceuticals, Inc.
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 2475
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides two human S100 proteins designated individually as S100P1 and S100P2 and collectively as S100P, and polynucleotides which identify and encode S100P. The invention also provides expression vectors, host cells, agonists, antibodies and antagonists. The invention also provides methods for treating disorders associated with expression of S100P.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 27 OF 29 USPATFULL
ACCESSION NUMBER: 97:24914 USPATFULL
TITLE: Method and compositions for modulating lifespan of hematolymphoid cells
INVENTOR(S): Weissman, Irving, Redwood City, CA, United States
Lagasse, Eric, Palo Alto, CA, United States
PATENT ASSIGNEE(S): Board of Trustees of the Leland Stanford Junior University, Stanford, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5614397		19970325	
APPLICATION INFO.:	US 1994-200016		19940222	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ketter, James S.
LEGAL REPRESENTATIVE: Bozicevic, Karl, Conley, Deirdre L.Fish & Richardson P.C.
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 20 Drawing Figure(s); 16 Drawing Page(s)
LINE COUNT: 1593
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods and compositions for modifying the lifespan of progeny cells of mammalian hematopoietic stem cells, particularly myeloid series cells, are provided. Transgenic nonhuman mammals also are provided which produce transgenic myeloid cells having an altered lifespan.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 28 OF 29 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93073121 EMBASE
DOCUMENT NUMBER: 1993073121
TITLE: Holocrine **secretion** of calprotectin: A neutrophil-mediated defense against Candida albicans?.
AUTHOR: Lehrer R.I.

```
CORPORATE SOURCE:   Department of Medicine, UCLA Center for the Health
                    Sciences,Los Angeles, CA 90024-1678, United States
SOURCE:             Journal of Laboratory and Clinical Medicine, (1993) 121/2
                    (193-194).
                    ISSN: 0022-2143  CODEN: JLCMAK
COUNTRY:            United States
DOCUMENT TYPE:      Journal; Editorial
FILE SEGMENT:       004     Microbiology
                    026     Immunology, Serology and Transplantation
                    029     Clinical Biochemistry
LANGUAGE:           English

L14    ANSWER 29 OF 29   PCTFULL   COPYRIGHT 2002 Univentio
****   DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER
****   DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER


=> s l14 and (intimal (w) injury (s) (blood (w) vessel?)
UNMATCHED LEFT PARENTHESIS 'AND (INTIMAL'
The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s l14 and (intimal (w) injury (s) (blood (w) vessel?))
L15         13 S L14
L16          0 FILE USPATFULL
L17         11 S L14
L18          0 FILE PCTFULL
L19          3 S L14
L20          1 FILE EUROPATFULL
L21          2 S L14
L22          0 FILE EMBASE
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L24          0 FILE BIOSIS
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L26          0 FILE BIOTECHNO
L27          0 S L14
L28          0 FILE CAPLUS
L29          0 S L14
L30          0 FILE ESBIOBASE
L31          0 S L14
L32          0 FILE MEDLINE
L33          0 S L14
L34          0 FILE SCISEARCH
L35          0 S L14
L36          0 FILE PATOSEP

TOTAL FOR ALL FILES
L37          1 L14 AND (INTIMAL (W) INJURY (S) (BLOOD (W) VESSEL?))

=> d l37 ibib abs
'ABS' IS NOT A VALID FORMAT FOR FILE 'EUROPATFULL'

The following are valid formats:


MAX -------- AN, ED, UP, EW, FS, TI, TIDE, TIFR, IN, PA, PAN, AG, AGN,
             OS, SO, DT, LA, DS, PIT, PI, OD, AI, PRAI, RLI, NTE, REP,
             REN, IC (ICM, ICS), ICA, ICI, CM, FA, GIS, PGC, CLMN, AB,
             ABDE, ABFR, DETD, DETDDE, DETDFR, CLMDE, CLMFR
MAXG ------- MAX plus GI
MAX.OS ----- MAX, OS only
MAXG.OS ---- MAX.OS plus GI
MAX.PS ----- MAX, PS only
IMAX ------- MAX, indented with text labels
IMAX.OS ---- MAX, indented with text labels, OS only
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IMAX.PS ---- MAX, indented with text labels, PS only

ALL -------- AN, ED, UP, EW, FS, TI, IN, PA, PAN, AG, AGN, OS, SO, DT,
             LA, DS, PIT, PI, OD, AI, PRAI, RLI, NTE, REP, REN, IC (ICM,
             ICS), ICA, ICI, CM, FA, GIS, PGC, CLMN, AB*,  DETD*, CLM*
             (* German or French text if English text is not available)
ALLG ------- ALL plus GI
ALL.OS ----- ALL, OS only
ALLG.OS ---- ALL.OS plus GI
ALL.PS ----- ALL, PS only
IALL ------- ALL, indented with text labels
IALLG ------ IALL plus GI
IALL.OS ---- ALL, indented with text labels, OS only
IALLG.OS --- IALL.OS plus GI
IALL.PS ---- ALL, indented with text labels, PS only

ALLDE ------ AN, ED, UP, EW, FS, TIDE, IN, PA, PAN, AG, AGN, OS, SO, DT,
             LA, DS, PIT, PI, OD, AI, PRAI, RLI, NTE, REP, REN, IC (ICM,
             ICS), ICA, ICI, CM, FA, GIS, PGC, CLMN, ABDE* , DETDDE*, CLMDE*
             (* English or French text if German text is not available)
ALLGDE ----- ALLDE plus GI
ALLDE.OS --- ALLDE, OS only
ALLGDE.OS -- ALLDE.OS plus GI
ALLDE.PS --- ALLDE, PS only

ALLFR ------ AN, ED, UP, EW, FS, TIFR, IN, PA, PAN, AG, AGN, OS, SO, DT,
             LA, DS, PIT, PI, OD, AI, PRAI, RLI, NTE, REP, REN, IC (ICM,
             ICS), ICA, ICI, CM, FA, GIS, PGC, CLMN, ABFR* , DETDFR*, CLMFR*
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ALLGFR ----- ALLFR plus GI
ALLFR.OS --- ALLFR, OS only
ALLGFR.OS -- ALLFR.OS plus GI
ALLFR.PS --- ALLFR, PS only

BRIEF ------ AN, ED, UP, EW, FS, TI, IN, PA, PAN, AG, AGN, OS, SO, DT,
             LA, DS, PIT, PI, OD, AI, PRAI, RLI, NTE, REP, REN, IC (ICM,
             ICS), ICA, ICI, CM, FA, GIS, PGC, CLMN, AB*, MCLM*
             (* German or French text if English text is not available)
BRIEFG ----- BRIEF plus GI
BRIEF.OS --- BRIEF, OS only
BRIEFG.OS -- BRIEF.OS plus GI
BRIEF.PS --- BRIEF, PS only
IBRIEF ----- BRIEF, indented with text labels
IBRIEFG ---- IBRIEF plus GI
IBRIEF.OS -- BRIEF, indented with text labels, OS only
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BIB -------- AN, ED, UP, EW, FS, TI, TIDE, TIFR, IN, PA, PAN, AG, AGN,
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BIB.OS ----- BIB, OS only
BIB.PS ----- BIB, PS only
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IBIB.OS ---- BIB, indented with text labels, OS only
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BIBU ------- BIB, with German headers
BIBU.OS ---- BIB, with German headers, OS only
BIBU.PS ---- BIB, with German headers, PS only

STD -------- AN, ED, UP, EW, FS, TI, TIDE, TIFR, IN, PA, SO, DS, PIT, PI,
             OD, AI, PRAI, RLI, NTE, REP, REN, IC (ICM, ICS), ICA, ICI
STD.OS ----- STD, OS only
STD.PS ----- STD, PS only
ISTD ------- STD, indented with text labels
ISTD.OS ---- STD, indented with text labels, OS only
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ISTD.PS ---- STD, indented with text labels, PS only
STDU ------- STD, with German headers
STDU.OS ---- STD, with German headers, OS only
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IND -------- ED, UP, EW, FS, IC (ICM, ICS), ICA, ICI
IND.OS ----- IND, OS only
IND.PS ----- IND, PS only

TRI -------- TI, TIDE, TIFR, IC (ICM, ICS), ICA, ICI, CLMN, PGC, FA, GIS
TRI.OS ----- TRI, OS only
TRI.PS ----- TRI, PS only

TX --------- DETD, CLM
TX.OS ------ TX, OS only
TX.PS ------ TX, PS only
TXDE ------- DETDDE, CLMDE
TXDE.OS ---- TXDE, OS only
TXDE.PS ---- TXDE, PS only
TXFR ------- DETDFR, CLMFR
TXFR.OS ---- TXFR, OS only
TXFR.PS ---- TXFR, PS only

To display a particular field or fields, enter the display field codes. For a list of display field codes, enter 'HELP DFIELDS' at an arrow prompt (=>). Examples of formats include: 'TI'; 'AN,TI,AU'; 'BIB,CT'; 'TI,CT'.
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L37 ANSWER 1 OF 1 EUROPATFULL COPYRIGHT 2002 WILA

PATENT APPLICATION

AN 1118681 EUROPATFULL ED 20010802 EW 200130 FS OS
TIEN METHOD FOR CONTROLLING THE RELEASE OF **GRANULES**.
IN SETO, Minoru, 572-33, Mitsuzawa, Fuji-shi, Sizuoka 417-0855, JP;
FUKUDA, Kouichirou, 282-1, Yunoki, Fuji-shi, Sizuoka 416-0908, JP
PA Asahi Kasei Kabushiki Kaisha, 2-6, Dojimahama 1-chome, Kita-ku,
Osaka-shi, Osaka 530-8205, JP
PAN 219576
AG Forstmeyer, Dietmar, Dr. rer. nat., Dipl.-Chem. et al., Boeters & Bauer,
Bereiteranger 15, 81541 Muenchen, DE
AGN 77023
OS BEPA2001058 EP 1118681 A1 0021
SO Wila-EPZ-2001-H30-T1a
DT Patent
LA Anmeldung in Japanisch; Veroeffentlichung in Englisch;
Verfahren in Englisch
DS R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE;
R IT; R LI; R LU; R MC; R NL; R PT; R SE
PIT EPA1 EUROPAEISCHE PATENTANMELDUNG (Internationale Anmeldung)
PI EP 1118681 A1 20010725
OD 20010725
AI EP 1999-944877 19990928
PRAI JP 1998-274574 19980929
RLI WO 99-JP5302 990928 INTAKZ
WO 0018970 000406 INTPNR
IC ICM C12Q003-00
ICS C07K014-47 C12Q001-02
CM I1

FA RLI; AG
ABEN; DETDEN; CLMEN
GI
GIS 6529
PGC 48
CLMN 11
ABEN The present invention is a very useful method of controlling **granule secretion** from neutrophils. The detecting method, screening method, or quantitative determination method of substances inhibiting or activating **granule secretion** based on the above method is very useful in providing therapeutic drugs for various diseases due to **intimal injury** of **blood vessels** brought about by **granules secretion** of neutrophil.

DETDEN TECHNICAL FIELD

The present invention relates to a method of controlling **secretion** of **granules** from cell lines having **granule secretion** capability, preferably **secretion** of **granules** from neutrophils and to a method of detecting substances which inhibit or activate the **granule secretion** reaction based on the method of controlling **secretion** of **granules**.

BACKGROUND ART

Neutrophils play an important role in the defense of a living body. A major function of neutrophils is to migrate into bacteria and microorganisms which invade into living bodies and eat the bacteria and microorganisms, thereby rendering a sterilizing effect. In one sterilization mechanism of neutrophils, sterilization is effected after fusion of phagosomes and **granules** by the action of bactericidal proteins and proteases which are present in the **granules**. Although bactericidal proteins and proteases which are present in neutrophils are important sterilization substances, their excessive production and **secretion** are known to injure intima of bloodvessels (Fahey, T. J. et al., In Update Pulmonary Diseases and Disorders (Fishman AP, ed) (1992) MacGraw-Hill, New York).

Intimal injury of **blood vessels** is deeply concerned with the occurrence of diseases such as adult respiratory distress syndrome (ARDS) (Weiland, J. E. et al., Am. Rev. Respir. Dis. (1986) 133: 218-225), injury by reperfusion after ischemia (Cavanagh, S. P. et al. Cardiovasc. Surg. (1998) 6: 112-118), glomerular nephritis (Jennette, J. C. and Falk, R. J., Am. J. Kidney Dis. (1994) 24: 130-141), cystic fibrosis (Greenberger, P. A., J. A. M. A (1997) 278: 1924-1930), rheumatoid arthritis (Chang, D. J. et al. Semin. Arthritis Rheum. (1996) 25: 390-403), chronic bronchitis (Hoidal, J. R., Semin. Respir. Infect. (1994) 9: 8-12), spasm of **blood vessel** (Merhi, Y. et al. Arterioscler. Thromb. (1993) 13: 951-957), asthma (Borson, D. B. et al. Am. J. Physiol. (1991) 260: L212-L225), peripheral circulation disorder and angina pectoris (Merhi, Y. et al. Arterioscler. Thromb. (1993) 13: 951-957), hypertension (Dz au, V. J., Am. J. Med. (1984) 77: 31-36), arteriosclerosis (Belch, J. J., Curr. Opin. Lipidol. (1994) 5: 440-446), and the like. Therefore, the substances which inhibit **secretion** of neutrophil **granules** are thought to be useful as a therapeutic drug for treating diseases associated with **secretion** of neutrophil **granules**. Genes which control **secretion** of neutrophil **granules** are also thought to make genetic therapy of diseases associated with **secretion** of neutrophil **granules** possible.

However, the mechanism of **secretion** of neutrophil

granules is not yet elucidated at present. An increase in the calcium concentration in neutrophils is known to be indispensable for **secretion** of **granules**. However, no molecules which are activated by an increase in the calcium concentration and induce **granule secretion** are known. Therefore, there have been no specific neutrophil **secretion** inhibitors developed so far, nor any genetic therapy targeting the inhibition of neutrophil **secretion** inhibitors practiced.

The study for specifying intra neutrophil molecules which are activated by the increase in the calcium concentration and researching compounds and genes which inhibit such molecules are expected to contribute to the development of an effective preventive and/or treating agent, and curative method for diseases associated with **secretion** of neutrophil **granules** such as adult respiratory distress syndrome (ARDS), injury by reperfusion after ischemia during acute myocardial infarction, glomerular nephritis, cystic fibrosis, rheumatoid arthritis, chronic bronchitis, cerebral vasospasm, asthma, peripheral circulation disorder, angina pectoris, hypertension, arteriosclerosis, and the like.

There are three types of **calgranulins: calgranulin** A (Burmeister, G., Immunology (1986) 171: 461-474) (named as S100A8, **MRP8**, p8, or L1 light chain), **calgranulin** B (Burmeister, G., Immunology (1986) 171: 461-474) (named as S100A9, **MRP14**, 14 or L1 heavy chain), and **calgranulin** C (Dell' Angelica, E. C., J. Biol. Chem. (1994) 269: 28929-28936) (named as S100A12 or p6).

Calgranulin A is a calcium-binding protein with a molecular weight of about 8 kD, **calgranulin** B is a calcium-binding protein with a molecular weight of about 14 kD, and **calgranulin** C is a calcium-binding protein with a molecular weight of about 10 kD and classified in the S100 protein.

Calgranulin A and **calgranulin** B were cloned by E. Lagasse et al. and their whole amino acid sequences were reported in 1988 (E. Lagasse and R. G. Clerc, Molc. Cellular. Biol. (1988) No. 8, 2402-2410). **Calgranulin** A and **calgranulin** B are present specifically in neutrophils and monocytes and occupy about 5% of all proteins in neutrophils or monocytes.

As a finding suggesting intracellular physiological functions of **calgranulins**, the action of **calgranulin** A and **calgranulin** B inhibiting the activity of casein kinases I and II has been reported (Murao S. et al. J. Biol. Chem (1989) 264: 8356-8360).

However, physiological functions of casein kinases I and II in neutrophils and monocytes are still to be clarified. This inhibitory effect is not dependent on the calcium concentration. Therefore, the physiological function through the activity control of casein kinases I and 11 by **calgranulin** A and **calgranulin** B is not known at the present. As the findings suggesting extracellular physiological functions of **calgranulins**, the function of **calgranulin** A to increase migration of neutrophils andmonocytes (Geczy, C. L., Biochim. Biophys. Acta (1996) 1313: 246-253) and the antibacterial activity of **calgranulin** A and **calgranulin** B (Murthy, A. R. K. et al., J. Immunol. (1993) 151: 6291-6301) have been reported.

However, the only **calgranulin** which exhibits neutrophil/monocyte migration activity is mouse calgranul in A. Thus, this is not a physiological activity common to other warm-blooded animals including humans. The antibacterial activity of **calgranulin** A and **calgranulin** B is due to their

capability of trapping divalent metals in a solution essential for the growth of bacteria. The activity would not be a physiological function specific to **calgranulins**.

Only little is known about physiological functions of **calgranulin** A and **calgranulin** B at the present time. The action of **calgranulin** A and **calgranulin** B to control **secretion** of neutrophil or monocyte **granules** has not been known at all. **Calgranulin** C was cloned by J. D. Gottsch et al. and its whole amino acid sequence was reported in 1997 (Gottsch, J. D. et al., Trans. Am. Ophthalmol. Soc. (1997). 95: 111-125). **Calgranulin** C is known to be present in granulocytes, but whether **calgranulin** C is present in other cells is not known. Neither, is its function known. Thus, the effect of **calgranulin** C on the control of the mechanism of neutrophil or monocyte **granule secretion** has not been known.

DISCLOSURE OF THE INVENTION

An object of the present invention is to provide a method of controlling **secretion** of **granules** of cell lines having **granule secretion** capability, and a method of detecting substances which inhibit or activate the reaction of **granule secretion** based on the method of controlling **secretion** of **granules**.

As a result of extensive studies to achieve the above objective, the inventors of the present invention have found that **secretion** of **granules** can be controlled in the following manner. Specifically, if a treatment to increase the amount of active form of **calgranulin** is carried out on a cell line having the capability of secreting **granules**, the cell line increases **secretion** of **granules**; and if a treatment to decrease the amount of active form of **calgranulin** is carried out, **granule secretion** from the cell line decreases. This finding has led to the completion of the present invention.

Specifically, the present invention provides a method of controlling **granule secretion** which comprises performing a treatment to increase or decrease an active form of **calgranulin** on a cell line having the capability of secreting **granules**.

The cell line having **granule secretion** capability used herein is not specifically limited inasmuch as the cell line can secrete **granules**. Neutrophils originating from warm-blooded animals or neutrophil-like cells can be given as preferable examples. Neutrophils originating from warm-blooded animals are also called neutrophilous leukocytes, neutrophilic leukocytes, heterophilic leukocytes, or polymorphonuclear leucocytes. Neutrophil-like cultured cells are cultured cells containing at least one type of **granule** included in neutrophils. HL60 cells that can be differentiated into granulocytes by a suitable treatment using retinoic acid, dimethylsulfoxide, or the like can be given as specific examples. Neutrophils can be separated from blood of the warm-blooded animals or cells which move into the abdominal cavity by stimulation such as intraperitoneal administration of casein (Biological Chemistry Experiment Lecture, second series, No. 8 Blood, Vol. 2, 679-685). Cultured leukemia cell strains which can be differentiated into granulocytes are used after induction into neutrophil-like cells by differentiation using a suitable inductor of differentiation (Biological Chemistry Experiment Lecture, second series, No. 8 Blood, Vol. 1, 117-123).

Calgranulins are present in warm-blooded animals, for example. **Calgranulin** A (named as S100A8, **MRP8**, p8, or L1 light

chain) and **calgranulin** B (named as S100A9, **MRP14**, p14 or L1 heavy chain) are known. Human-type **calgranulin** A and human-type **calgranulin** B were cloned and their whole amino acid sequences have been reported (E. Lagasse and R. G. Clerc, Molc. Cellular. Biol. (1988) No. 8, 2402-2410). Mouse-type **calgranulin** A and mouse-type **calgranulin** B were cloned and their whole amino acid sequences have been reported (E. Lagasse and I. L. Weissman, Blood (1992) 79: 1907-1915). Mouse-type **calgranulin** A and mouse-type **calgranulin** B show a high homology of amino acid sequence to those of humans. Specifically, their homology to the human-type **calgranulin** A and human-type **calgranulin** B, respectively, is about 60%. **Calgranulin** A and **calgranulin** B which are present in various warm-blooded animals are thought to exhibit comparatively small difference in the amino acid sequence among animals. Therefore, in the **calgranulin** of the present invention the amino acid sequences exhibiting about 60% or more homology to the amino acid sequence of human **calgranulin** A or B are included in the preferable peptides as long as the amino acid sequences possess the following preferable activity.

In the present invention, a **calgranulin** exhibiting activity is specially referred to as an active form of **calgranulin**. Specifically, such activity may be any activity based on **calgranulin** A or **calgranulin** B, and this can be easily confirmed by the following measuring method of **calgranulin** activity.

Specifically, the **calgranulin** activity can be easily confirmed and determined by using the method shown in Example 1 or 2. The permeabilized neutrophil suspension prepared by the method of Example 1 is added to a 96-well immunoplate and incubated at 30-40.degree.C for 5-30 minutes. After simultaneous or successive addition of a water-soluble calcium compound and a substance having **calgranulin** activity to the well, the **calgranulin** activity is determined by measuring the amount of substances secreted in the supernatant, such as elastase or lactoferrin, according to the method of Example 1 or 2.

In a normal case, an active form of **calgranulin** is produced by binding **calgranulin** and calcium.

Homologues or mixtures of **calgranulins** are also included in the **calgranulin** of the present invention.

Homologues of **calgranulin** A or **calgranulin** B are mutants, fragments, and derivatives of the **calgranulins** possessing **calgranulin** activity. The mutants indicate **calgranulins** exhibiting the same activity as the **calgranulin** A or **calgranulin** B, but formed by a natural or artificial gene manipulation technique on a DNA level, for example, by the site specific mutagenesis, in which a part of amino acids is replaced, deleted, or added (PAS, 75, pp 4268-4270 (1978), Necl. Acid. Res., 6, pp 2973-2985 (1979), Genetic Engineering Principle and Methods, Vol. 3, pp 1-32 (1981), etc.).

The fragments mean fragments of **calgranulin** A or **calgranulin** B which contains continuous amino acids.

The derivatives mean **calgranulin** A or **calgranulin** B in which the functional group such as an amino group, hydroxyl group, mercapto group, or carboxyl group is modified by, for example, glycosylation, acylation, amidation, or esterification. The derivatives further include dimers of **calgranulin** A or **calgranulin** B, their mutants, or fragments in which the mercapto group of cysteine residue is oxidized to the disulfide form providing intermolecular S-S

linkages, as well as mixed dimers produced from **calgranulin** A, its mutant, or fragment and **calgranulin** B, its mutant, or fragment which are bound through an oxidized mercapto group of cysteine residue, all exhibiting the **calgranulin** activity.

There are no limitations to the mixtures inasmuch as the mixture is a mixture of **calgranulin** A or its homologue and **calgranulin** B or its homologue at an arbitrary ratio and exhibits the **calgranulin** activity.

The amino acid sequence of **calgranulin** A is shown by Sequence ID No. 1 of the Sequence Table (Nature (1987) 330 (5) 80-82), and the amino acid sequence of **calgranulin** B is shown by Sequence ID No. 2 of the Sequence Table (the same source) . Therefore, **calgranulins** including at least one of the following peptides can be given as preferable active form of **calgranulins** of the present invention.

(i) A peptide consisting of the amino acid sequence 1-93 of Sequence ID No. 1 of the Sequence Table and binding calcium thereto.

(ii) A peptide consisting of the amino acid sequence 1-114 of Sequence ID No. 2 of the Sequence Table and binding calcium thereto.

(iii) A peptide having an amino acid sequence in which one or more amino acids are deleted from or added to the amino acid sequence of Sequence ID No. 1 or 2 of the Sequence Table, or one or more amino acids in the amino acid sequence of Sequence ID No. 1 or 2 are replaced with other amino acids, binding calcium thereto, and exhibiting the activity of increasing **secretion** of **granules** of cell lines having **granule secretion** capability.

The following methods can be given as examples of the method of increasing an active form of **calgranulin** in cell lines having **granule secretion** capability.

a) A method of converting cell membranes of cell lines having **granule secretion** capability, preferably neutrophils or neutrophil-like cultured cells into permeabilized cell membranes, and simultaneously or successively adding a **calgranulin** and a water-soluble calcium compound.

b) A method of simultaneously or successively adding a **calgranulin** and a water-soluble calcium compound to a cell line having **granule secretion** capability by microinjection using a very fine injection needle.

c) A method of mixing a **calgranulin** and a water-soluble calcium compound, enclosing the mixture in a liposome, and causing the mixture to contact with a cell line having **granule secretion** capability, thereby fusing cell membranes.

d) A method of introducing a **calgranulin** gene into a cell line having **granule secretion** capability to cause **calgranulin** to over expression and adding a water-soluble calcium compound to the expressed **calgranulin**.

To change the membrane of a cell line having **granule secretion** capability into a permeabilized cell membrane, cells having **granule secretion** capability are first separated from blood, for example and prepared. Any known method of separation and preparation may be used for preparing such cells. The cells having **granule secretion** capability may be suspended cells or may occasionally be adhered cells. Suspended cells are more preferable in the present invention in view of ease of separation from blood. Cells having **granule secretion** capability separated from blood are suspended and stored in a physiological saline solution or a phosphate buffered saline.

When used, the suspension is re-suspended in a buffer solution containing potassium chloride and sodium chloride such as a HEPES buffer solution or Tris buffer solution, for example, incubated, and processed

to convert the membranes into permeabilized cell membranes. A buffer solution containing 50-200 mM potassium chloride and 5-30 mM sodium chloride is preferable as the buffer solution containing potassium chloride and sodium chloride used in the present invention. Specific examples are a 10-50 mM HEPES (pH 6.5-7.5) buffer solution or a 10-50 mM Tris (pH 6.5-7.5) buffer solution. The mixture is incubated at 4-40.degree.C for 10-60 minutes.

The cells having **granule secretion** capability separated from blood are incubated in a RPMI 1640 medium, MEM medium, or the like which contains fetal bovine serum. Suspended cells are re-suspended in the buffer solution containing potassium chloride and sodium chloride. In the case of adhered cells, supernatant of the culture liquid is discarded and cells are re-suspended in the buffer solution containing potassium chloride and sodium chloride. The suspension is incubated in the same manner as described above and processed to make the membranes permeabilized cell membranes.

The cells having **granule secretion** capability obtained in this manner are subjected to a treatment to make the membranes permeabilized cell membranes. One example of this treatment comprises treating the cells with an agent having a function of making holes through the membranes by acting on part of the cell membranes such as, for example, a surfactant, bacterial toxin, or glycerol. As examples of surfactants, digitonin, saponin, octylphenol-polyethyleneglycolether (Triton X-100), 3-[(3-cholamidopropyl)dimethylammoniol]-1-propane-sulfonate (CHAPS) , polyoxyethylene (20) cetylether (Brij 58), and the like can be given. As examples of bacterial toxins, .alpha.-toxin, streptolysin-O, and the like can be given. An amount of 0.01 .mu.M to 1000 mM of the above agent is added to 1 x 10.sup7. cells/ml, and the mixture is incubated at 4-40.degree.C for 5-120 minutes.

Treatment of cells using short electric pulses (an electroporation method) is another preferable method of forming permeabilized cell membranes. Specifically, an amount of 1 x 10.sup7. cells/ml of cell line is treated with 1-10 KV electric pulses at 4-40.degree.C for 1-30 minutes.

Amethod of using laser beams, a method of using a hypotonic solution, and the like are also preferable methods of forming permeabilized cell membranes.

The water-soluble calcium compound used in the present invention is not specifically limited inasmuch as the compound produces calcium ions when it contacts with water. Powders or aqueous solutions of calcium acetate, calcium carbonate, and calcium chloride are given as examples. Aparticularly preferable water-soluble calcium compound is a compound which produces calcium ions at a concentration of 100 mM or more when the compound contacts with water. When an aqueous solution is used, its calcium concentration is preferably 100 mM or more.

Simultaneous addition of a **calgranulin** and a water-soluble calcium compound to permeabilized cell membranes in the present invention means a procedure of previously mixing the **calgranulin** and water-soluble calcium compound, incubating the mixture to make the **calgranulin** active form of, and adding the active form of **calgranulin**. Successive addition of a **calgranulin** and a water-soluble calcium compound means a procedure of separately adding the **calgranulin** and water-soluble calcium compound irrespective of the order of addition.

The amount of **calgranulin** added is usually 0.01 .mu.M or more, and preferably 0.1-5 .mu.M. Although there is no specific upper limit, an amount less than 10 .mu.M is preferable. In the same manner, the amount of water-soluble calcium compound added is usually 0.01 .mu.M or

more, and preferably 0.1-5 .mu.M. Although there is no specific upper limit, the amount less than 10 .mu.M is preferable.

Incubation is carried out usually at 4-40.degree.C. Incubation is carried out usually for 5-30 minutes.

The other methods of increasing an active form of **calgranulin** in cell lines having **granule secretion** capability will now be described.

Cells having **granule secretion** capability are first separated from blood, and suspended and stored in a physiological saline or a phosphate buffered saline as mentioned above. Alternatively, the cells are cultured in a RPMI medium, MEM medium, or the like containing fetal bovine serum. In the case of suspended cells, the cells are suspended in a culture medium. In the case of adhered cells, the cells are need for microinjection, introduction of liposomes, genes, and the like.

Although microinjection is carried out according to a conventional method, the use of a very fine injection needle with a diameter of usually 1 .mu.m or less, preferably 0.1-0.8 .mu.m, is desirable. Such an injection needle can be prepared by extending a molten glass capillary. Specifically, an injection needle is set in a manipulator controllable within an accuracy of 1 .mu.m, and a **calgranulin** and a soluble calcium compound are simultaneously microinjected into the cells. Alternatively, the **calgranulin** is microinjected first and, after a while, for example after 1-60 minutes, preferably after 3-10 minutes, the water-soluble calcium compound is microinjected. It is possible to microinject **calgranulin** after microinjection of the water-soluble calcium compound. In this instance, the concentrations of the **calgranulin** and water-soluble calcium compound may be approximately the same as the above described concentrations.

In the method of increasing an active form of **calgranulin** in a cell line having **granule secretion** capability by membrane fusing using a liposome, the **calgranulin** and a water-soluble calcium compound are mixed and enclosed in the liposome, and caused to contact with the cells, thereby fusing cell membranes. First, a phospholipid solution containing cholesterol, for example, a mixture of egg yolk phosphatidylcholin, dimyristoyl phosphatidic acid, and cholesterol at a molar ratio of 4:1:5 is prepared. A water-soluble calcium compound and **calgranulin** are added to the mixture, and the resulting mixture is stirred and filtered through a membrane filter, for example, a membrane filter made of Teflon, thereby obtaining an emulsion. The emulsion is subjected to a rotary evaporator to evaporate an organic solvent, and **calgranulin** which is not enclosed in the liposome is removed. As the method of removal, a 12% sucrose density-gradient centrifugation is preferably used. In this manner, **calgranulin** is mixed with a water-soluble calcium compound and converted into an active form of **calgranulin**, and a liposome in which the active form of **calgranulin** is enclosed prepared. Next, the liposome with an active form of **calgranulin** is enclosed therein is caused to contact with the above-mentioned cells having **granule secretion** capability. For example, the liposome is added to 1x10.sup5. 1x10.sup7. cells in a concentration of 0.01-100 .mu.M, and preferably 0.1-10 .mu.M, and the mixture is incubated. Incubation is carried out at 4-40.degree.C for 1-30 minutes, for example. In this manner, membranes are fused and an active form of **calgranulin** can be increased in the cell lines having **granule secretion** capability.

As a method of causing **calgranulin** to over-expression, a method of recombining a gene encoding **calgranulin** in a known

plasmid vector or virus vector, and introducing the recombinant into the cells can be given. The base sequence shown as Sequence ID No. 1 or No. 2 in the sequence table, for example, can be used as a gene encoding **calgranulin**. The recombinant vector can be introduced into the cells by the calcium phosphate method, the DEAE dextranmethod, lipofectinmethod, electricpulsemethod, or the like. The above-described various methods may be preferably used for introducing a **calgranulin** gene in a cell line and causing the **calgranulin** to over-expression. The cells are converted to cells having the above-mentioned permeabilized cell membrane and a water-soluble calcium compound is preferably introduced in the cell line. Specifically, a **calgranulin** gene is introduced into cells by incubating a plasmid vector or virus vector in which the **calgranulin** gene has been incorporated in the amount of the 1-200 .mu.g per 0.5x10.sup7. to 3x10.sup7. cells at 4-40.degree.C for 5-120 minutes together with 1-100 .mu.g of calcium phosphate, 0.1-10 mg of DEAE dextran, or 1-100 .mu.g of lipofectin, or by treating the plasmid vector or virus vector in which the **calgranulin** gene has been incorporated in the amount of the 1-200 .mu.g per 0.5x10.sup7. to 3x10.sup7. cells using a short electric pulse at 4-40.degree.C for 1-30 minutes. The above-mentioned various methods may be used for introducing the water-soluble calcium compound.

The following methods can be given as examples of the method of decreasing active form of **calgranulin** of cell lines having **granule secretion** capability.

a) A method of converting a cell line having **granule secretion** capability into cells with permeabilized cell membranes and adding a **calgranulin** antibody.

b) A method of adding **calgranulin** antibody to a cell line having **granule secretion** capability by microinjection using a very fine injection needle.

c) A method of enclosing a **calgranulin** antibody in a liposome and causing the liposome to act on a cell line having **granule secretion** capability, thereby fusing cell membranes.

d) A method of introducing an anti-sense gene for a **calgranulin** gene into a cell line having **granule secretion** capability, thereby knocking out **calgranulin**.

A monoclonal antibody to **calgranulin** can be prepared by the method described in Am. J. Physiol. 274, C1563-C1572 (1988). For example, 10-100 .mu. g of **calgranulin** is mixed with a complete Freund's adjuvant and intraperitoneally administered in a mouse, After administration several times, once every two weeks, the spleen is excised to prepare spleen cells. The spleen cells are fused with myeloma cells using polyethylene glycol and cultured in an HAT medium containing 15% fetal bovine serum, to select only fused cells. At the time when colonies are identified by the naked eye, **calgranulin** antibody-producing cells are confirmed by the ELISA method in which the **calgranulin** is combined with a 96 well immuno plate, and cloning is carried out by the limiting dilution method. The cells obtained are cultured and the monoclonal antibody to **calgranulin** produced in the supernatant is collected.

The monoclonal antibody to **calgranulin** is also available from BMA Company.

To obtain a polyclonal antibody to **calgranulin**, 10-100 .mu.g of **calgranulin** is mixed with a complete Freund's adjuvant and subcutaneously administered to a rabbit. After administration several times, once every two weeks, blood is collected to obtain a polyclonal antibody as antiserum.

The **calgranulin** antibody is added to the cells having **granule secretion** capability having permeabilized cell membranes prepared by the above-mentioned method in an amount of 1-100 .mu.g per 1x10.sup5. to 1x10.sup7. cells, for example, and the mixture is incubated at 4-40.degree.C for 1-30 minutes, whereby the **calgranulin** antibody is introduced into the cells.

Microinjection is another method of introducing **calgranulin** antibody into cell lines, wherein 0.01-10 .mu.g of the **calgranulin** antibody is introduced into the cells by microinjection using an injection needle set in a manipulator under pressure by an injector.

Still another method comprises enclosing 1-100 .mu.g of the **calgranulin** antibody into the above-mentioned liposome, adding the liposome to the cells at a concentration of 0.01-100 .mu.M, preferably 0.1-10 .mu.M, per 1x10.sup5. to 1x10.sup7. cells, and incubating the mixture at 4-40.degree.C for 1-30 minutes.

A **calgranulin** anti-sense gene can be obtained by inserting a gene having a base sequence complementary to the base sequence shown by Sequence ID No. 1 or No. 2, for example. In the present invention, a plasmid vector or virus vector is prepared by insertingl-200 .mu.g of this **calgranulin** anti-sense gene per 0.5x10.sup7. to 3x10.sup7. cells. The resulting vector is incubated at 4-40.degree.C for 5-120 minutes with the addition of 1-100 .mu.g of calcium phosphate, 0.1-10 mg of DEAE dextran, or 1-100 .mu.g of lipofectin. Alternatively, a plasmid vector or virus vector with 1-200 .mu.g of the **calgranulin** anti-sense gene inserted per 0.5x10.sup7. to 3x10.sup7. cells is added and treated by a short electric pulse at 0.05-0.5 kV at a temperature of 4-40.degree.C for 1-30 minutes.

In this manner, an anti-sense gene for a **calgranulin** gene is introduced into a cell line having **granule secretion** capability and knocked out.

A treatment of increasing or decreasing an active form of **calgranulin** in cell lines having **granule secretion** capability can be carried out according to the above-described procedure. As a result, **granule secretion** of a cell line can be controlled by increasing or decreasing **granule secretion** of the cell line.

Granule secretion of neutrophils is known to injure intima of blood vessels as mentioned above. Injury of blood vessel intima is known to be deeply associated with diseases such as adult respiratory distress syndrome (ARDS), injury by reperfusion after ischemia during acute myocardial infarction, glomerular nephritis, cystic fibrosis, rheumatoid arthritis, chronic bronchitis, cerebral vasospasm, asthma, peripheral circulation disorder, angina pectoris, hypertension, arteriosclerosis,and the like. Therefore, a curative agent, improving agent, or improving method may be provided when **granule secretion** is decreased in the above method for controlling **secretion** of **granule**. A gene therapy for diseases and phenomenon associated with **secretion** of neutrophil **granules**, such as adult respiratory distress syndrome (ARDS), injury by reperfusion after ischemia during acute myocardial infarction, glomerular nephritis, cystic fibrosis, rheumatoid arthritis, chronic bronchitis, cerebral spasm, asthma, peripheral circulation disorder, angina pectoris, hypertension, arteriosclerosis, and the like, maybe possible if an anti-sense gene for a **calgranulin** gene is recombined in virus vector introducing the resultant recombinant gene into neutrophils removed from a patient and returning the cells to the patient. Specifically, the above-described **granule secretion** control method includes a curative

method and improving method of the above diseases.

The present invention also provides a method of detecting a substance which inhibits or activates the **granule secretion** reaction.

Specifically, the present invention provides a method of detecting a substance which inhibits or activates the **granule secretion** reaction comprising the following steps:

A) A step of increasing an active form of **calgranulin** in cell lines having **granule secretion** capability;

B) A stepof causing a sample which may contain a substance inhibiting or activating the **granule secretion** reaction (hereinafter simply referred to as "sample") to contact with the cell lines having **granule secretion** capability, and incubating the mixture; and

C) A step of detecting the subject substance secreted from the cell line.

The step B) for causing the sample to contact with the cell lines having **granule secretion** capability may be carried out before, after, or during the step A) for increasing an active form of **calgranulin**.

The method of detecting a substance which inhibits or activates the **granule secretion** reaction of the present invention includes a method of quantitative determination of the substance or a method of screening the substance.

The same procedure as described above can be employed in the method of conducting the step A) to increase active form of **calgranulin** of cell lines having **granule secretion** capability. Specifically, the following methods can be given:

a) A method of converting cell membranes of cell lines having **granule secretion** capability, preferably neutrophils or neutrophil-like cultured cells, into permeabilized cell membranes, and simultaneously or successively adding a **calgranulin** and a water-soluble calcium compound.

b) A method of simultaneously or successively adding a **calgranulin** and a water-soluble calcium compound to a cell line having **granule secretion** capability by microinjection using a very fine injection needle.

c) A method of mixing a **calgranulin** and a water-soluble calcium compound, enclosing the mixture in a liposome, and causing the mixture to come into contact with a cell line having **granule secretion** capability to fuse cell membranes.

d) A method of introducing a **calgranulin** gene into a cell line having **granule secretion** capability to cause the **calgranulin** to be over-expressed and adding a water-soluble calcium compound to the expressed **calgranulin**.

In the step B) of causing a sample which may contain a substance inhibiting or activating the **granule secretion** reaction to contact with the cell lines having **granule secretion** capability, and incubating the mixture, biological components, naturally occurring substances, compounds, and the like can be given as examples of the sample. This procedure of causing the sample to contact with the cell lines having **granule secretion** capability is carried out before, after, or during the step A) of increasing an active form of **calgranulin**. As the cell lines having **granule secretion** capability, the said cell line having **granule secretion** capability itself, a cell line in which the **calgranulin** has been increased, a cell line in which the active form of **calgranulin** has been increased, and the like can be used. The former two cell lines

increase an active form of **calgranulin** by the above-mentioned treatment for increasing the active form of **calgranulin**.

In a preferable method of increasing an active form of **calgranulin**, the **calgranulin** is first increased in the cell line having **granule secretion** capability and then a water-soluble calcium compound is increased in this cell line, or an active form of **calgranulin** produced by reacting a **calgranulin** with a water-soluble calcium compound is increased in the cell line having **granule secretion** capability. This sample is caused to contact with the cell line before, after, or during the procedure of increasing the **calgranulin** or active form of **calgranulin**. The procedure of contacting the sample with the cell line is preferable as a method of screening pharmaceutical agents without a treatment in which the sample is penetrated through cell membranes.

A specific example is as follows. In the case where permeabilized cell membranes are used, an appropriate concentration of the sample which may contain a substance inhibiting or activating the **granule secretion** reaction is added to the cell suspension and the mixture is incubated. In this instance, 1-100 .mu.M of the sample is added to a suspension of neutrophils or neutrophil-like cultured cells having permeabilized cell membranes, and the mixture is incubated at 4-40.degree.C for 1-30 minutes. Next, a **calgranulin** is added, and after a while, a water-soluble calcium compound is added. For example, the water-soluble calcium compound is added 1-60 minutes, and preferably 3-10 minutes, after the addition of **calgranulin**. In this instance, the **calgranulin** and water-soluble calcium compound are added in the amount of about 0.01-10 .mu.M each and preferably 0.1-3 .mu.M each. The order of the addition may be either first **calgranulin** and then water-soluble calcium compound, or first the water-soluble calcium compound and then the **calgranulin**. The most preferable method is first preparing an active form of **calgranulin** by the reaction of a **calgranulin** and a water-soluble calcium compound, then adding the active form of **calgranulin** into the above mentioned cell line. The sample may be added to the cell line not only before the addition of the **calgranulin**, but also simultaneously or after the addition of the **calgranulin** or active form of **calgranulin**. The reaction for **granule secretion** is initiated in this manner.

In the case where cells having **granule secretion** capability, for example, neutrophils or neutrophil-like cultured cells are injected by microinjection, an appropriate concentration, for example, 1-100 .mu.M, of the sample which may contain a substance inhibiting or activating the **granule secretion** reaction is added to the neutrophils or neutrophil-like cultured cells, and the mixture is incubated at 4-40.degree.C for 1-30 minutes. A **calgranulin** is microinjected at an appropriate concentration, for example, at 0.01-10 .mu.M, and preferably 0.1-3 .mu.M, and a water-soluble calcium compound is microinjected simultaneously at a concentration, for example, at 0.01-10 .mu.M, and preferably 0.1-3 .mu.M. Alternatively, the water-soluble calcium compound is microinjected after microinjection of **calgranulin**, for example after 1-60 minutes, preferably after 3-10 minutes, whereby the **granule secretion** reaction is initiated.

In the case where neutrophils or neutrophil-like cultured cells are reacted with a liposome, a sample which may contain a substance inhibiting or activating the **granule secretion** reaction is added to the suspension of the neutrophils or neutrophil-like cultured cells at an appropriate concentration, 1-100 .mu.M, for example, and the mixture is incubated for 1-30 minutes. A

calgranulin is previously mixed with a water-soluble calcium compound at a concentration of, for example, 0.01-10 .mu.M, and preferably 0.1-3 .mu.M, and the mixture is incubated, for example, at 4-40.degree.C for 1-30 minutes, then introduced into a liposome at a concentration of 0.01-10 .mu.M, and preferably 0.1-3 .mu.M. The liposome is added into a suspension of neutrophils or neutrophil-like cultured cells to initiate the **granule secretion** reaction.

In the case of using cells in which the **calgranulin** is over-expressed, for example neutrophils or neutrophil-like cultured cells into which a **calgranulin** gene has been introduced, an appropriate concentration of sample which may contain a substance inhibiting or activating the **granule secretion** reaction is incubated for 1-30 minutes, for example. A water-soluble calcium compound is added at a concentration of, for example, 0.01-10 .mu.M, and preferably 0.1-3 .mu.M, and the mixture is incubated for 1-30 minutes, for example. Then calcium ionophore, for example, A23187 or ionomycin, is added at a concentration of 0.01-10 .mu.M, and preferably 0.1-3 .mu.M to initiate the **granule secretion** reaction.

Next, the step C) for detecting the subject substance secreted from the cell line is carried out.

Azurophil **granules** (primary **granules**) , specific **granules** (secondary **granules**) , and storage **granules** (tertiary **granules**) are given as **granules** contained in neutrophils. Acidic .beta. -glycerophosphatase, .beta.-glucuronidase, N-acetyl-.beta. -glucurosaminidase, .alpha.- mannosidase, arylsulfatase, .beta. -galactosidase, .alpha.-fucosidase, cathepsin B, cathepsin D, cathepsin G, elastase, proteinase 3, myeloperoxidase, lysozyme, and the like are secreted from Azurophil **granules**. Collagenase, lysozyme, lactoferrin, vitamin B.sub12.-binding protein, cytochrome b, and the like are secreted from the special **granules**. Gelatinase, N-acetyl-.beta.-glucurosaminidase, cathepsin B, cathepsin D,.beta.-glucuronidase, .beta.-glycerophosphatase, -mannosidase, and the like are secreted from storage **granules**. These substances can be selected as a subject substance to be detected. Each of the subject substances can be quantitatively analyzed by means of an appropriate method.

For example, the quantity of myeloperoxidase secreted from Azurophil **granules** can be determined from the rate of increase in the absorbance at 650 nm by a spectrophotometer using 3,3',5,5'-tetramethylbenzidine and a hydrogen peroxide as substrates. Lactoferrin secreted from specific **granules** can be determined by ELISA (enzyme-linked immunoassay, an assay kit manufactured by Oxis Co.) using an antilactoferrin antibody. The quantity of N-acetyl-.beta.-glucurosaminidase, .beta. -glucuronidase, and .alpha.-mannosidase secreted from storage **granules** can be determined by measuring 4-methylunberiferil which is produced by the hydrolysisof a 4-methylunberiferil derivative (Sigma Co.) as a substrate using fluorescence spectrophotometer at an excitation wavelength of 365 nm and a fluorescence wavelength 450 nm.

The method of detection of a substance which may inhibit or activate the **granule secretion** reaction according to the present invention can be carried out in this manner. Therefore, a substance which inhibits or activates the **granule secretion** reaction contained in the above-mentioned sample can be quantitatively determined.

A preferable example of the quantitative determination of the present invention is as follows.

The target substance (sample) which is an object of screening is caused to be present at an appropriate concentration in a suspension of neutrophils or neutrophil-like cultured cells having permeabilized cell membranes, and a **calgranulin** and a water-soluble calcium compound are added to make an appropriate concentration, respectively, to measure the amount of secreted **granules**. For example, 5x10.sup6. cells/ml to 5x10.sup7. cells/ml of human neutrophils which are treated with digitonin to make the membrane permeabilized membranes is prepared. A sample is added to a concentration of 1-100 .mu.M, followed by the addition of **calgranulin** A (0.01-10 .mu.M, preferably 0.1-3 .mu.M) and an aqueous solution of calcium chloride compound (0.01-10 .mu.M, preferably 0.1-3 .mu.M). The mixture is incubated at 25-40.degree.C, preferably 30-70.degree.C, for 1-60 minutes, and preferably for 5-15 minutes. As examples of the medium used in this incubation buffer solution (pH:about 7-7.4) containing, 100 mM - 200 mM potassium chloride, 10 mM - 20 mM sodium chloride, and 0.3 mM - 3 mM EGTA, for example, phosphoric acid, MOPS, HEPES, Tris, TAPA, BES, and TES buffer containing them can be given. The amount of the substance secreted during the incubation is determined and compared with a control to which no sample is added.

According to the present invention a method of screening a **calgranulin** activity activator, which is used for increasing **calgranulin** activity of neutrophils or neutrophil-like cultured cells and then increasing **granule secretion**, can be provided. Specifically, a substance (sample) which is an object of the screening is selected and caused to be present in a suspension of neutrophils or neutrophil-like cultured cells having permeabilized cell membranes at an appropriate concentration (1-100 .mu.M, for example). A water-soluble calcium compound at an appropriate concentration (for example, 0.01-10 .mu.M, and preferably 0.1-3 .mu.M) and a **calgranulin**, for example **calgranulin** A, at an appropriate concentration (for example, 0.01-10 .mu.M, and preferably 0.1-3 .mu.M) are added to the suspension, thereby screening the substance which increases the quantity of **granules secretion** even more.

A simple method of screening a **calgranulin** activity deactivator can be provided by the method of activating the activity of **calgranulin** permeable through cell membranes of neutrophils or neutrophil-like cultured cells of the present invention. Specifically, a substance (sample) which is an object of screening is selected and caused to be present in a suspension of cultured neutrophils or neutrophil-like cells at an appropriate concentration (1-100 .mu.M, for example). A **calgranulin** activity activator at an appropriate concentration (for example, 0.01-100 .mu.M, and preferably 0.1-10 .mu.M) is added to the suspension, thereby screening the substance which inhibits **granules secretion**.

Granule secretion of neutrophils is known to injure intima of **blood vessels** as mentioned above. Injury of **blood vessel** intima is known to be deeply associated with diseases such as adult respiratory distress syndrome (ARDS), injury by reperfusion after ischemia during acute myocardial infarction, glomerular nephritis, cystic fibrosis, rheumatoid arthritis, chronic bronchitis, cerebral vasospasm, asthma, peripheral circulation disorder, angina pectoris, hypertension, arteriosclerosis, and the like. Therefore, the above method of screening the neutrophil **granule secretion** inhibitor can be applied to the screening of a substance which inhibits the **intimal injury** of **blood vessels**.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an elastase **secretion** reaction of human neutrophils having high permeability cell membranes by **calgranulin** A in Example 1.

Figure 2 shows an elastase **secretion** reaction of human neutrophils having high permeability cell membranes by **calgranulin** B in Example 1.

Figure 3 shows an elastase **secretion** reaction of human neutrophils having high permeability cell membranes by a mixture of **calgranulin** A and **calgranulin** B in Example 1.

Figure 4 shows a lactoferrin **secretion** reaction of human neutrophils having high permeability cell membranes by **calgranulin** A in Example 2.

Figure 5 shows a lactoferrin **secretion** reaction of human neutrophils having high permeability cell membranes by **calgranulin** B in Example 2.

Figure 6 shows a lactoferrin **secretion** reaction of human neutrophils having high permeability cell membranes by a mixture of **calgranulin** A and **calgranulin** B in Example 2.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention will now describedmore specifically by way of examples. However, the present invention is not limited to these following examples.

Example 1

<Method of controlling elastase **secretion** from human neutrophils according to an increase or decrease of **calgranulin** content>

Elastase is a typical **secretion** substance which is present in primary **granules** of neutrophils. Elastase is a proteinase which decomposes elastin, an elastic protein present in blood vessels, etc., and causes hindrance to occur. A method of controlling elastase **secretion** by **calgranulin** using human neutrophils will be described.

A neutrophil suspension was prepared from blood collected from human vein according to the method described in Biological Chemistry Experiment Lecture, second series, No. 8, Blood, Vol. 2, 679-685). The neutrophil suspension was adjusted to a concentration of 1x10.sup7. cells/ml in a plastic test tube using a permeabilized buffer (PB) (30 mM HEPES, 100 mM KCl, 20 mM NaCl, 1 mM EGTA, pH 7.0) and incubated at 37.degree.C for 10 minutes. Digitonin (Sigma company) was added to the neutrophil suspension to a final concentration of 5-7.5 .mu.g/ml and the mixture was incubated at 37.degree.C for 15 minutes. The neutrophil suspension was centrifuged at 1200 rpm for 5 minutes. After discarding supernatant, precipitated neutrophils were re-suspended in PB to prepare a permeabilized neutrophil suspension (cell concentration: 1x10.sup7./ml).

The permeabilized neutrophil suspension was added to a 96-well immunoplate, 200 .mu.l per well, and incubated for at 37.degree.C 15 minutes. Next, an aqueous solution of calcium chloride (final concentration: 1 .mu.M) and **calgranulin** A, **calgranulin** B, or a equimolar mixture of **calgranulin** A and **calgranulin** B (each to a final concentration of 0 .mu.M, 0.3 .mu.M, 1 .mu.M, or 3 .mu.M) were added, and the resulting mixture was incubated at 37.degree.C for 5 minutes.

The 96-well immunoplate was centrifuged at 1200 rpm for one minute at 4.degree.C using a centrifugation container for immunoplates. The supernatant is transferred to another 96-well immunoplate, 160 .mu.l per well, and incubated at 37.degree.C for 5 minutes. 10 mM of an elastase substrate (Suc-Ala-Pro-Ala-pNA, Peptide Laboratory, Inc.) was added to the 96-well immunoplate. After gently shaking, the mixture was incubated at 37.degree.C for 30 minutes. Then, absorbance at 405 nm was measured using a microplate reader.

The results are shown in Figure 1 (**calgranulin** A) , Figure 2 (**calgranulin** B) , and Figure 3 (a mixture of **calgranulin** A and **calgranulin** B). **Calgranulin** A increased elastase **secretion** from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 1). Assuming that the amount of elastase **secretion** in the absence of **calgranulin** A is 1, 3 .mu.M of **calgranulin** A remarkably increased the amount of elastase **secretion** (about eight times).

Calgranulin B increased elastase **secretion** from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 2). Assuming that the amount of elastase **secretion** in the absence of **calgranulin** B is 1, 3 .mu.M of **calgranulin** B remarkably increased the amount of elastase **secretion** (about seven times). A mixture of **calgranulin** A and **calgranulin** B increased elastase **secretion** from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 3). Assuming that the amount of elastase **secretion** in the absence of the mixture is 1, 3 .mu.M of the mixture of **calgranulin** A and **calgranulin** B remarkably increased the amount of elastase **secretion** (about six times).

These results show that change in the amount of **calgranulin** A, **calgranulin** B, or a mixture of **calgranulin** A and **calgranulin** B in neutrophils can remarkably change the amount of elastase **secretion**.

Example 2

<Method of controlling lactoferrin **secretion** from human neutrophils according to an increase or decrease of **calgranulin** content>

Lactoferrin is a typical **secretion** substance which is present in secondary **granules** of neutrophils. A method of controlling lactoferrin **secretion** by **calgranulin** using human neutrophils will be described.

A neutrophil suspension was prepared from blood collected from human vein according to the method described in Biological Chemistry Experiment Lecture, second series, No. 8, Blood, Vol. 2, 679-685). The neutrophil suspension was adjusted to a concentration of 1x10.sup7. cells/ml using PB in a plastic test tube and incubated at 37.degree.C for 10 minutes. Digitonin (Sigma company) was added to the neutrophil suspension to a final concentration of 5 .mu.g/ml and the mixture was incubated at 37.degree.C for 15 minutes.

The neutrophil suspension was centrifuged at 1200 rpm for 5 minutes. After supernatant was discarded, precipitated neutrophils were re-suspended in PB to prepare a permeabilized neutrophil suspension (cell concentration: 1x10.sup7. cells/ml). The permeabilized neutrophil suspension was added to a 96-well immunoplate, 200 .mu.l per well, and incubated at 37.degree.C for 15 minutes. Next, an aqueous solution of

calcium chloride (final concentration: 1 .mu.M) and **calgranulin** A, **calgranulin** B, or a equimolar mixture of **calgranulin** A and **calgranulin** B (each to a final concentration of 0 .mu.M, 0.3 .mu.M, 1 .mu.M, or 3 .mu.M) were added, and the resulting mixtures were incubated at 37.degree.C for 5 minutes. The 96-well immunoplate was centrifuged at 1200 rpm for one minute at 4.degree.C. ELISA-kit (OXIS Co.) was used for the determination of lactoferrin. The results are shown in Figures 4, 5, and 6. **Calgranulin** A increased lactoferrin **secretion** from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 4). Assuming that the amount of lactoferrin **secretion** in the absence of **calgranulin** A is 1, 3 .mu.M of **calgranulin** A remarkably increased the amount of lactoferrin **secretion** (about six times) . **Calgranulin** B increased lactoferrin **secretion** from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 5). Assuming that the amount of lactoferrin **secretion** in the absence of **calgranulin** B is 1, 3 .mu.M of **calgranulin** B remarkably increased the amount of lactoferrin **secretion** (about five times) . Amixture of **calgranulin** A and **calgranulin** B increased lactoferrin **secretion** from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 6) . Assuming that the amount of lactoferrin **secretion** in the absence of the mixture is 1, 3 .mu.M of the mixture of **calgranulin** A and **calgranulin** B remarkably increased the amount of lactoferrin **secretion** (about five times).

These results show that change in the amount of **calgranulin** A, **calgranulin** B, or a mixture of **calgranulin** A and **calgranulin** B in neutrophils can remarkably change the amount of lactoferrin **secretion**.

The results of Examples 1 and 2 show that **calgranulins** are important proteins to control **granule secretion** form neutrophils.

Example 3

<Method of Screening a substance inhibiting or activating **granule secretion** by allowing a sample to stand in the system in which the amount of elastase **secretion** from neutrophils is greatly increased by changing **calgranulin** activity>

A neutrophil suspension was prepared from blood collected from a human vein according to the method described in Biological Chemistry Experiment Lecture, second series, No. 8, Blood, Vol. 2, 679-685). The neutrophil suspension was adjusted to a concentration of 1x10.sup7. cells/ml using PB in a plastic test tube and incubated at 37.degree.C for 10 minutes. Digitonin was added to the neutrophil suspension to a final concentration of 5 .mu.g/ml and the mixture was incubated at 37.degree.C for 15 minutes. The neutrophil suspension was centrifuged at 1200 rpm for 5 minutes.

After supernatant was discarded, the precipitate was re-suspended in PB to prepare a permeabilized neutrophil suspension (cell concentration: 1x10.sup7. cells/ml). The permeabilized neutrophil suspension was added to a 96-well immunoplate, 200 .mu.l per well, and incubated at 37.degree.C for 15 minutes. N-(4-methoxybenzyl)-N-(4-methoxyphenyl)-7-piperazinylheptyl amine trihydrochloride (Compound 1), N-benzyl-N-(4-methoxyphenyl)-7-piperazinylheptylamine trihydrochloride (Compound 2), 1,1-(di-4-hydroxyphenyl)-2-ethyl-1-octaene (Compound 3), and 2-hydroxy-5-((-4-((-2-pyridinylamino)sulfonyl)phenyl)azo)be nzoic acid (Compound 4) were used as samples for screening.

These samples were added to a final concentration of 30 .mu.M and the mixtures were incubated at 37.degree.C for 15 minutes. Next, an aqueous solution of calcium chloride (final concentration: 1 .mu.M) and **calgranulin** A, **calgranulin** B, or a equimolar mixture of **calgranulin** A and **calgranulin** B (each to a final concentration of 0 .mu.M, 0.3 .mu.M, 1 .mu.M, or 3 .mu.M) were added, and the resulting mixtures were incubated at 37.degree.C for 5 minutes. The 96-well immunoplate was centrifuged at 1200 rpm for one minute at 4.degree.C using a centrifugal separator for immunoplates. The supernatant is transferred to another 96-well immunoplate and incubated at 37.degree.C for 5 minutes. 10 mM of an elastase substrate (Suc-Ala-Pro-Ala-pNA) was added to the 96-well immunoplate. After gently shaking, the mixture was incubated at 37.degree.C for 30 minutes. Then, absorbance at 405 nm was measured using a microplate reader.

The results are shown in Table 1. The **secretion** inhibiting rate of samples was determined by comparison with a control which does not contain the screening sample, assuming that the **secretion** from the control is 100%. Compound 1 and Compound 2 increased the activity of **calgranulin** A and remarkably controlled **granule secretion** in a system in which the amount of elastase **secretion** from neutrophils has been remarkably increased. Compound 3 remarkably increased the amount of **secretion** in the above system. <table>

INDUSTRIAL APPLICABILITY

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CLMEN 1. A method of controlling **granule secretion** comprising performing a treatment to increase or decrease an active form of **calgranulin** on a cell line having **granules secretion** capability, thereby increasing or decreasing **granule secretion** from the cell line.

2. The method according to claim 1, wherein the cell line having **granule secretion** capability is neutrophils or neutrophil-like cultured cells originating from a warm-blooded animal.

3. The method according to claim 1 or claim 2, wherein the active form of **calgranulin** is one or more of the following peptides:

(i) A peptide consisting of the amino acid sequence 1-93 of Sequence ID No. 1 of the Sequence Table and binding calcium thereto,

(ii) A peptide consisting of the amino acid sequence 1-114 of Sequence ID No. 2 of the Sequence Table and binding calcium thereto, and

(iii) A peptide having an amino acid sequence in which one or more amino acids are deleted from or added to the amino acid sequence of Sequence ID No. 1 or 2 of the Sequence Table, or one or more amino acids in the amino acid sequence of Sequence ID No. 1 or 2 are replaced with other amino acids, binding calcium thereto, and exhibiting the activity of increasing **secretion** of **granules** of cell lines having **granule secretion** capability.

4. A method of detecting a substance which inhibits or activates a **granule secretion** reaction comprising the following steps:

A) a step of increasing an active form of **calgranulin** in cell lines having **granule secretion** capability;

B) a step of causing a sample which may contain a substance inhibiting or activating the **granule secretion** reaction to contact with the cell lines having **granule secretion** capability before, after, or during the step A) , and incubating the mixture; and

C) a step of detecting the subject substance secreted from the cell

line.

5. A method according to claim 4, wherein the step A) of increasing an active form of **calgranulin** in a cell line having the capability of secreting **granules** comprises successively carrying out the following steps a) and b):

a) a step of changing the cell line having **granule secretion** capability into a permeabilized cell; and

b) a step of simultaneously or successively adding a **calgranulin** and a water-soluble calcium compound to the cell line and incubating the cell line.

6. The method according to claim 4 or claim 5, wherein the cell line having **granule secretion** capability is neutrophils originating from a warm-blooded animal or neutrophil-like cultured cells.

7. The method according to any one of claims 4-6, wherein the active form of **calgranulin** is one or more of the following peptides:

(i) A peptide consisting of the amino acid sequence 1-93 of Sequence ID No. 1 of the Sequence Table and binding calcium thereto,

(ii) A peptide consisting of the amino acid sequence 1-114 of Sequence ID No. 2 of the Sequence Table and binding calcium thereto, and

(iii) A peptide having an amino acid sequence in which one or more amino acids are deleted from or added to the amino acid sequence of Sequence ID No. 1 or 2 of the Sequence Table, or one or more amino acids in the amino acid sequence of Sequence ID No. 1 or 2 are replaced with other amino acids, binding calcium thereto, and exhibiting the activity of increasing **secretion** of **granules** of cell lines having **granule secretion** capability.

8. The method according to claim 5, wherein the water-soluble calcium compound is a solution or powder of a compound which produces calcium ions at a concentration of 100 mM or more when the compound contacts with water.

9. The method according to any one of claims 4-8, wherein the method of detection is a quantitative determination method.

10. The method according to any one of claims 4-8, wherein the method of detection is a screening method.

11. A method of obtaining a substance for controlling **intimal injury** of **blood vessels** comprising acquiring the substance for controlling **intimal injury** of **blood vessels** by screening a substance inhibiting **granule secretion** reaction by the method of claim 10.

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PATENT APPLICATION

AN 1118681 EUROPATFULL ED 20010802 EW 200130 FS OS
TIEN METHOD FOR CONTROLLING THE RELEASE OF **GRANULES**.
IN SETO, Minoru, 572-33, Mitsuzawa, Fuji-shi, Sizuoka 417-0855, JP;
FUKUDA, Kouichirou, 282-1, Yunoki, Fuji-shi, Sizuoka 416-0908, JP
PA Asahi Kasei Kabushiki Kaisha, 2-6, Dojimahama 1-chome, Kita-ku,
Osaka-shi, Osaka 530-8205, JP
PAN 219576
AG Forstmeyer, Dietmar, Dr. rer. nat., Dipl.-Chem. et al., Boeters & Bauer,
Bereiteranger 15, 81541 Muenchen, DE
AGN 77023
OS BEPA2001058 EP 1118681 A1 0021
SO Wila-EPZ-2001-H30-T1a
DT Patent
LA Anmeldung in Japanisch; Veroeffentlichung in Englisch;
Verfahren in Englisch
DS R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE;
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PIT EPA1 EUROPAEISCHE PATENTANMELDUNG (Internationale Anmeldung)
PI EP 1118681 A1 20010725
OD 20010725
AI EP 1999-944877 19990928
PRAI JP 1998-274574 19980929
RLI WO 99-JP5302 990928 INTAKZ
WO 0018970 000406 INTPNR
IC ICM C12Q003-00
ICS C07K014-47 C12Q001-02
CM I1
FA RLI; AG
ABEN; DETDEN; CLMEN
GI
GIS 6529
PGC 48
CLMN 11
ABEN The present invention is a very useful method of controlling **granule secretion** from neutrophils. The detecting method, screening method, or quantitative determination method of substances inhibiting or activating **granule secretion** based on the above method is very useful in providing therapeutic drugs for various diseases due to intimal injury of blood vessels brought about by **granules secretion** of neutrophil.

DETDEN TECHNICAL FIELD

The present invention relates to a method of controlling secretion of **granules** from cell lines having **granule secretion** capability, preferably secretion of **granules** from neutrophils and to a method of detecting substances which inhibit or activate the **granule secretion** reaction based on the method of controlling secretion of **granules**.

BACKGROUND ART

Neutrophils play an important role in the defense of a living body. A major function of neutrophils is to migrate into bacteria and microorganisms which invade into living bodies and eat the bacteria and microorganisms, thereby rendering a sterilizing effect. In one sterilization mechanism of neutrophils, sterilization is effected after fusion of phagosomes and **granules** by the action of bactericidal proteins and proteases which are present in the

granules. Although bactericidal proteins and proteases which are present in neutrophils are important sterilization substances, their excessive production and secretion are known to injure intima of bloodvessels (Fahey, T. J. et al., In Update Pulmonary Diseases and Disorders (Fishman AP, ed) (1992) MacGraw-Hill, New York).

Intimal injury of blood vessels is deeply concerned with the occurrence of diseases such as adult respiratory distress syndrome (ARDS) (Weiland, J. E. et al., Am. Rev. Respir. Dis. (1986) 133: 218-225), injury by reperfusion after ischemia (Cavanagh, S. P. et al. Cardiovasc. Surg. (1998) 6: 112-118), glomerular nephritis (Jennette, J. C. and Falk, R. J., Am. J. Kidney Dis. (1994) 24: 130-141), cystic fibrosis (Greenberger, P. A., J. A. M. A (1997) 278: 1924-1930), rheumatoid arthritis (Chang, D. J. et al. Semin. Arthritis Rheum. (1996) 25: 390-403), chronic bronchitis (Hoidal, J. R., Semin. Respir. Infect. (1994) 9: 8-12), spasm of blood vessel (Merhi, Y. et al. Arterioscler. Thromb. (1993) 13: 951-957), asthma (Borson, D. B. et al. Am. J. Physiol. (1991) 260: L212-L225), peripheral circulation disorder and angina pectoris (Merhi, Y. et al. Arterioscler. Thromb. (1993) 13: 951-957), hypertension (Dz au, V. J., Am. J. Med. (1984) 77: 31-36), arteriosclerosis (Belch, J. J., Curr. Opin. Lipidol. (1994) 5: 440-446), and the like. Therefore, the substances which inhibit secretion of neutrophil **granules** are thought to be useful as a therapeutic drug for treating diseases associated with secretion of neutrophil **granules**. Genes which control secretion of neutrophil **granules** are also thought to make genetic therapy of diseases associated with secretion of neutrophil **granules** possible.

However, the mechanism of secretion of neutrophil **granules** is not yet elucidated at present. An increase in the calcium concentration in neutrophils is known to be indispensable for secretion of **granules**. However, no molecules which are activated by an increase in the calcium concentration and induce **granule secretion** are known. Therefore, there have been no specific neutrophil secretion inhibitors developed so far, nor any genetic therapy targeting the inhibition of neutrophil secretion inhibitors practiced.

The study for specifying intra neutrophil molecules which are activated by the increase in the calcium concentration and researching compounds and genes which inhibit such molecules are expected to contribute to the development of an effective preventive and/or treating agent, and curative method for diseases associated with secretion of neutrophil **granules** such as adult respiratory distress syndrome (ARDS), injury by reperfusion after ischemia during acute myocardial infarction, glomerular nephritis, cystic fibrosis, rheumatoid arthritis, chronic bronchitis, cerebral vasospasm, asthma, peripheral circulation disorder, angina pectoris, hypertension, arteriosclerosis, and the like.

There are three types of **calgranulins**: **calgranulin** A (Burmeister, G., Immunology (1986) 171: 461-474) (named as S100A8, MRP8, p8, or L1 light chain), **calgranulin** B (Burmeister, G., Immunology (1986) 171: 461-474) (named as S100A9, MRP14, 14 or L1 heavy chain), and **calgranulin** C (Dell' Angelica, E. C., J. Biol. Chem. (1994) 269: 28929-28936) (named as S100A12 or p6).

Calgranulin A is a calcium-binding protein with a molecular weight of about 8 kD, **calgranulin** B is a calcium-binding protein with a molecular weight of about 14 kD, and **calgranulin** C is a calcium-binding protein with a molecular weight of about 10 kD and classified in the S100 protein.

Calgranulin A and **calgranulin** B were cloned by E. Lagasse et al. and their whole amino acid sequences were reported in 1988 (E. Lagasse and R. G. Clerc, Molc. Cellular. Biol. (1988) No. 8, 2402-2410). **Calgranulin** A and **calgranulin** B are

present specifically in neutrophils and monocytes and occupy about 5% of all proteins in neutrophils or monocytes.

As a finding suggesting intracellular physiological functions of **calgranulins**, the action of **calgranulin** A and **calgranulin** B inhibiting the activity of casein kinases I and II has been reported (Murao S. et al. J. Biol. Chem (1989) 264: 8356-8360).

However, physiological functions of casein kinases I and II in neutrophils and monocytes are still to be clarified. This inhibitory effect is not dependent on the calcium concentration. Therefore, the physiological function through the activity control of casein kinases I and 11 by **calgranulin** A and **calgranulin** B is not known at the present. As the findings suggesting extracellular physiological functions of **calgranulins**, the function of **calgranulin** A to increase migration of neutrophils andmonocytes (Geczy, C. L., Biochim. Biophys. Acta (1996) 1313: 246-253) and the antibacterial activity of **calgranulin** A and **calgranulin** B (Murthy, A. R. K. et al., J. Immunol. (1993) 151: 6291-6301) have been reported.

However, the only **calgranulin** which exhibits neutrophil/monocyte migration activity is mouse calgranul in A. Thus, this is not a physiological activity common to other warm-blooded animals including humans. The antibacterial activity of **calgranulin** A and **calgranulin** B is due to their capability of trapping divalent metals in a solution essential for the growth of bacteria. The activity would not be a physiological function specific to **calgranulins**.

Only little is known about physiological functions of **calgranulin** A and **calgranulin** B at the present time. The action of **calgranulin** A and **calgranulin** B to control secretion of neutrophil or monocyte **granules** has not been known at all. **Calgranulin** C was cloned by J. D. Gottsch et al. and its whole amino acid sequence was reported in 1997 (Gottsch, J. D. et al., Trans. Am. Ophthalmol. Soc. (1997). 95: 111-125). **Calgranulin** C is known to be present in granulocytes, but whether **calgranulin** C is present in other cells is not known. Neither, is its function known. Thus, the effect of **calgranulin** C on the control of the mechanism of neutrophil or monocyte **granule secretion** has not been known.

DISCLOSURE OF THE INVENTION

An object of the present invention is to provide a method of controlling secretion of **granules** of cell lines having **granule secretion** capability, and a method of detecting substances which inhibit or activate the reaction of **granule secretion** based on the method of controlling secretion of **granules**.

As a result of extensive studies to achieve the above objective, the inventors of the present invention have found that secretion of **granules** can be controlled in the following manner. Specifically, if a treatment to increase the amount of active form of **calgranulin** is carried out on a cell line having the capability of secreting **granules**, the cell line increases secretion of **granules**; and if a treatment to decrease the amount of active form of **calgranulin** is carried out, **granule secretion** from the cell line decreases. This finding has led to the completion of the present invention.

Specifically, the present invention provides a method of controlling **granule secretion** which comprises performing a treatment to increase or decrease an active form of **calgranulin** on a cell line having the capability of secreting **granules**.

The cell line having **granule secretion** capability used herein is not specifically limited inasmuch as the cell line can secrete **granules**. Neutrophils originating from warm-blooded animals or neutrophil-like cells can be given as preferable examples. Neutrophils originating from warm-blooded animals are also called neutrophilous leukocytes, neutrophilic leukocytes, heterophilic leukocytes, or polymorphonuclear leucocytes. Neutrophil-like cultured cells are cultured cells containing at least one type of **granule** included in neutrophils. HL60 cells that can be differentiated into granulocytes by a suitable treatment using retinoic acid, dimethylsulfoxide, or the like can be given as specific examples. Neutrophils can be separated from blood of the warm-blooded animals or cells which move into the abdominal cavity by stimulation such as intraperitoneal administration of casein (Biological Chemistry Experiment Lecture, second series, No. 8 Blood, Vol. 2, 679-685). Cultured leukemia cell strains which can be differentiated into granulocytes are used after induction into neutrophil-like cells by differentiation using a suitable inductor of differentiation (Biological Chemistry Experiment Lecture, second series, No. 8 Blood, Vol. 1, 117-123).

Calgranulins are present in warm-blooded animals, for example. **Calgranulin** A (named as S100A8, MRP8, p8, or L1 light chain) and **calgranulin** B (named as S100A9, MRP14, p14 or L1 heavy chain) are known. Human-type **calgranulin** A and human-type **calgranulin** B were cloned and their whole amino acid sequences have been reported (E. Lagasse and R. G. Clerc, Molc. Cellular. Biol. (1988) No. 8, 2402-2410). Mouse-type **calgranulin** A and mouse-type **calgranulin** B were cloned and their whole amino acid sequences have been reported (E. Lagasse and I. L. Weissman, Blood (1992) 79: 1907-1915). Mouse-type **calgranulin** A and mouse-type **calgranulin** B show a high homology of amino acid sequence to those of humans. Specifically, their homology to the human-type **calgranulin** A and human-type **calgranulin** B, respectively, is about 60%. **Calgranulin** A and **calgranulin** B which are present in various warm-blooded animals are thought to exhibit comparatively small difference in the amino acid sequence among animals. Therefore, in the **calgranulin** of the present invention the amino acid sequences exhibiting about 60% or more homology to the amino acid sequence of human **calgranulin** A or B are included in the preferable peptides as long as the amino acid sequences possess the following preferable activity.

In the present invention, a **calgranulin** exhibiting activity is specially referred to as an active form of **calgranulin**. Specifically, such activity may be any activity based on **calgranulin** A or **calgranulin** B, and this can be easily confirmed by the following measuring method of **calgranulin** activity.

Specifically, the **calgranulin** activity can be easily confirmed and determined by using the method shown in Example 1 or 2. The permeabilized neutrophil suspension prepared by the method of Example 1 is added to a 96-well immunoplate and incubated at 30-40.degree.C for 5-30 minutes. After simultaneous or successive addition of a water-soluble calcium compound and a substance having **calgranulin** activity to the well, the **calgranulin** activity is determined by measuring the amount of substances secreted in the supernatant, such as elastase or lactoferrin, according to the method of Example 1 or 2.

In a normal case, an active form of **calgranulin** is produced by binding **calgranulin** and calcium.

Homologues or mixtures of **calgranulins** are also included in

the **calgranulin** of the present invention.

Homologues of **calgranulin** A or **calgranulin** B are mutants, fragments, and derivatives of the **calgranulins** possessing **calgranulin** activity. The mutants indicate **calgranulins** exhibiting the same activity as the **calgranulin** A or **calgranulin** B, but formed by a natural or artificial gene manipulation technique on a DNA level, for example, by the site specific mutagenesis, in which a part of amino acids is replaced, deleted, or added (PAS, 75, pp 4268-4270 (1978), Necl. Acid. Res., 6, pp 2973-2985 (1979), Genetic Engineering Principle and Methods, Vol. 3, pp 1-32 (1981), etc.).

The fragments mean fragments of **calgranulin** A or **calgranulin** B which contains continuous amino acids.

The derivatives mean **calgranulin** A or **calgranulin** B in which the functional group such as an amino group, hydroxyl group, mercapto group, or carboxyl group is modified by, for example, glycosylation, acylation, amidation, or esterification. The derivatives further include dimers of **calgranulin** A or **calgranulin** B, their mutants, or fragments in which the mercapto group of cysteine residue is oxidized to the disulfide form providing intermolecular S-S linkages, as well as mixed dimers produced from **calgranulin** A, its mutant, or fragment and **calgranulin** B, its mutant, or fragment which are bound through an oxidized mercapto group of cysteine residue, all exhibiting the **calgranulin** activity.

There are no limitations to the mixtures inasmuch as the mixture is a mixture of **calgranulin** A or its homologue and **calgranulin** B or its homologue at an arbitrary ratio and exhibits the **calgranulin** activity.

The amino acid sequence of **calgranulin** A is shown by Sequence ID No. 1 of the Sequence Table (Nature (1987) 330 (5) 80-82), and the amino acid sequence of **calgranulin** B is shown by Sequence ID No. 2 of the Sequence Table (the same source) . Therefore, **calgranulins** including at least one of the following peptides can be given as preferable active form of **calgranulins** of the present invention.

(i) A peptide consisting of the amino acid sequence 1-93 of Sequence ID No. 1 of the Sequence Table and binding calcium thereto.

(ii) A peptide consisting of the amino acid sequence 1-114 of Sequence ID No. 2 of the Sequence Table and binding calcium thereto.

(iii) A peptide having an amino acid sequence in which one or more amino acids are deleted from or added to the amino acid sequence of Sequence ID No. 1 or 2 of the Sequence Table, or one or more amino acids in the amino acid sequence of Sequence ID No. 1 or 2 are replaced with other amino acids, binding calcium thereto, and exhibiting the activity of increasing secretion of **granules** of cell lines having **granule secretion** capability.

The following methods can be given as examples of the method of increasing an active form of **calgranulin** in cell lines having **granule secretion** capability.

a) A method of converting cell membranes of cell lines having **granule secretion** capability, preferably neutrophils or neutrophil-like cultured cells into permeabilized cell membranes, and simultaneously or successively adding a **calgranulin** and a water-soluble calcium compound.

b) A method of simultaneously or successively adding a **calgranulin** and a water-soluble calcium compound to a cell line having **granule secretion** capability by microinjection using a very fine injection needle.

c) A method of mixing a **calgranulin** and a water-soluble calcium compound, enclosing the mixture in a liposome, and causing the

mixture to contact with a cell line having **granule secretion** capability, thereby fusing cell membranes.

d) A method of introducing a **calgranulin** gene into a cell line having **granule secretion** capability to cause **calgranulin** to over expression and adding a water-soluble calcium compound to the expressed **calgranulin**.

To change the membrane of a cell line having **granule secretion** capability into a permeabilized cell membrane, cells having **granule secretion** capability are first separated from blood, for example and prepared. Any known method of separation and preparation may be used for preparing such cells. The cells having **granule secretion** capability may be suspended cells or may occasionally be adhered cells. Suspended cells are more preferable in the present invention in view of ease of separation from blood. Cells having **granule secretion** capability separated from blood are suspended and stored in a physiological saline solution or a phosphate buffered saline.

When used, the suspension is re-suspended in a buffer solution containing potassium chloride and sodium chloride such as a HEPES buffer solution or Tris buffer solution, for example, incubated, and processed to convert the membranes into permeabilized cell membranes. A buffer solution containing 50-200 mM potassium chloride and 5-30 mM sodium chloride is preferable as the buffer solution containing potassium chloride and sodium chloride used in the present invention. Specific examples are a 10-50 mM HEPES (pH 6.5-7.5) buffer solution or a 10-50 mM Tris (pH 6.5-7.5) buffer solution. The mixture is incubated at 4-40.degree.C for 10-60 minutes.

The cells having **granule secretion** capability separated from blood are incubated in a RPMI 1640 medium, MEM medium, or the like which contains fetal bovine serum. Suspended cells are re-suspended in the buffer solution containing potassium chloride and sodium chloride. In the case of adhered cells, supernatant of the culture liquid is discarded and cells are re-suspended in the buffer solution containing potassium chloride and sodium chloride. The suspension is incubated in the same manner as described above and processed to make the membranes permeabilized cell membranes.

The cells having **granule secretion** capability obtained in this manner are subjected to a treatment to make the membranes permeabilized cell membranes. One example of this treatment comprises treating the cells with an agent having a function of making holes through the membranes by acting on part of the cell membranes such as, for example, a surfactant, bacterial toxin, or glycerol. As examples of surfactants, digitonin, saponin, octylphenol-polyethyleneglycolether (Triton X-100), 3-[(3-cholamidopropyl)dimethylammoniol]-1-propane-sulfonate (CHAPS) , polyoxyethylene (20) cetylether (Brij 58), and the like can be given. As examples of bacterial toxins, .alpha.-toxin, streptolysin-O, and the like can be given. An amount of 0.01 .mu.M to 1000 mM of the above agent is added to 1 x 10.sup7. cells/ml, and the mixture is incubated at 4-40.degree.C for 5-120 minutes.

Treatment of cells using short electric pulses (an electroporation method) is another preferable method of forming permeabilized cell membranes. Specifically, an amount of 1 x 10.sup7. cells/ml of cell line is treated with 1-10 KV electric pulses at 4-40.degree.C for 1-30 minutes.

Amethod of using laser beams, a method of using a hypotonic solution, and the like are also preferable methods of forming permeabilized cell membranes.

The water-soluble calcium compound used in the present invention is not specifically limited inasmuch as the compound produces calcium ions when

it contacts with water. Powders or aqueous solutions of calcium acetate, calcium carbonate, and calcium chloride are given as examples. Aparticularly preferable water-soluble calcium compound is a compound which produces calcium ions at a concentration of 100 mM or more when the compound contacts with water. When an aqueous solution is used, its calcium concentration is preferably 100 mM or more.

Simultaneous addition of a **calgranulin** and a water-soluble calcium compound to permeabilized cell membranes in the present invention means a procedure of previously mixing the **calgranulin** and water-soluble calcium compound, incubating the mixture to make the **calgranulin** active form of, and adding the active form of **calgranulin**. Successive addition of a **calgranulin** and a water-soluble calcium compound means a procedure of separately adding the **calgranulin** and water-soluble calcium compound irrespective of the order of addition.

The amount of **calgranulin** added is usually 0.01 .mu.M or more, and preferably 0.1-5 .mu.M. Although there is no specific upper limit, an amount less than 10 .mu.M is preferable. In the same manner, the amount of water-soluble calcium compound added is usually 0.01 .mu.M or more, and preferably 0.1-5 .mu.M. Although there is no specific upper limit, the amount less than 10 .mu.M is preferable.

Incubation is carried out usually at 4-40.degree.C. Incubation is carried out usually for 5-30 minutes.

The other methods of increasing an active form of **calgranulin** in cell lines having **granule secretion** capability will now be described.

Cells having **granule secretion** capability are first separated from blood, and suspended and stored in a physiological saline or a phosphate buffered saline as mentioned above. Alternatively, the cells are cultured in a RPMI medium, MEM medium, or the like containing fetal bovine serum. In the case of suspended cells, the cells are suspended in a culture medium. In the case of adhered cells, the cells are need for microinjection, introduction of liposomes, genes, and the like.

Although microinjection is carried out according to a conventional method, the use of a very fine injection needle with a diameter of usually 1 .mu.m or less, preferably 0.1-0.8 .mu.m, is desirable. Such an injection needle can be prepared by extending a molten glass capillary. Specifically, an injection needle is set in a manipulator controllable within an accuracy of 1 .mu.m, and a **calgranulin** and a soluble calcium compound are simultaneously microinjected into the cells. Alternatively, the **calgranulin** is microinjected first and, after a while, for example after 1-60 minutes, preferably after 3-10 minutes, the water-soluble calcium compound is microinjected. It is possible to microinject **calgranulin** after microinjection of the water-soluble calcium compound. In this instance, the concentrations of the **calgranulin** and water-soluble calcium compound may be approximately the same as the above described concentrations.

In the method of increasing an active form of **calgranulin** in a cell line having **granule secretion** capability by membrane fusing using a liposome, the **calgranulin** and a water-soluble calcium compound are mixed and enclosed in the liposome, and caused to contact with the cells, thereby fusing cell membranes. First, a phospholipid solution containing cholesterol, for example, a mixture of egg yolk phosphatidylcholin, dimyristoyl phosphatidic acid, and cholesterol at a molar ratio of 4:1:5 is prepared. A water-soluble calcium compound and **calgranulin** are added to the mixture, and the resulting mixture is stirred and filtered through a membrane filter,

for example, a membrane filter made of Teflon, thereby obtaining an emulsion. The emulsion is subjected to a rotary evaporator to evaporate an organic solvent, and **calgranulin** which is not enclosed in the liposome is removed. As the method of removal, a 12% sucrose density-gradient centrifugation is preferably used. In this manner, **calgranulin** is mixed with a water-soluble calcium compound and converted into an active form of **calgranulin**, and a liposome in which the active form of **calgranulin** is enclosed prepared. Next, the liposome with an active form of **calgranulin** is enclosed therein is caused to contact with the above-mentioned cells having **granule secretion** capability. For example, the liposome is added to 1x10.sup5. 1x10.sup7. cells in a concentration of 0.01-100 .mu.M, and preferably 0.1-10 .mu.M, and the mixture is incubated. Incubation is carried out at 4-40.degree.C for 1-30 minutes, for example. In this manner, membranes are fused and an active form of **calgranulin** can be increased in the cell lines having **granule secretion** capability.

As a method of causing **calgranulin** to over-expression, a method of recombining a gene encoding **calgranulin** in a known plasmid vector or virus vector, and introducing the recombinant into the cells can be given. The base sequence shown as Sequence ID No. 1 or No. 2 in the sequence table, for example, can be used as a gene encoding **calgranulin**. The recombinant vector can be introduced into the cells by the calcium phosphate method, the DEAE dextranmethod, lipofectinmethod, electricpulsemethod, or the like. The above-described various methods may be preferably used for introducing a **calgranulin** gene in a cell line and causing the **calgranulin** to over-expression. The cells are converted to cells having the above-mentioned permeabilized cell membrane and a water-soluble calcium compound is preferably introduced in the cell line. Specifically, a **calgranulin** gene is introduced into cells by incubating a plasmid vector or virus vector in which the **calgranulin** gene has been incorporated in the amount of the 1-200 .mu.g per 0.5x10.sup7. to 3x10.sup7. cells at 4-40.degree.C for 5-120 minutes together with 1-100 .mu.g of calcium phosphate, 0.1-10 mg of DEAE dextran, or 1-100 .mu.g of lipofectin, or by treating the plasmid vector or virus vector in which the **calgranulin** gene has been incorporated in the amount of the 1-200 .mu.g per 0.5x10.sup7. to 3x10.sup7. cells using a short electric pulse at 4-40.degree.C for 1-30 minutes. The above-mentioned various methods may be used for introducing the water-soluble calcium compound.

The following methods can be given as examples of the method of decreasing active form of **calgranulin** of cell lines having **granule secretion** capability.

a) A method of converting a cell line having **granule secretion** capability into cells with permeabilized cell membranes and adding a **calgranulin** antibody.

b) A method of adding **calgranulin** antibody to a cell line having **granule secretion** capability by microinjection using a very fine injection needle.

c) A method of enclosing a **calgranulin** antibody in a liposome and causing the liposome to act on a cell line having **granule secretion** capability, thereby fusing cell membranes.

d) A method of introducing an anti-sense gene for a **calgranulin** gene into a cell line having **granule secretion** capability, thereby knocking out **calgranulin**

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A monoclonal antibody to **calgranulin** can be prepared by the method described in Am. J. Physiol. 274, C1563-C1572 (1988). For example, 10-100 .mu. g of **calgranulin** is mixed with a complete Freund's adjuvant and intraperitoneally administered in a mouse, After administration several times, once every two weeks, the spleen is

excised to prepare spleen cells. The spleen cells are fused with myeloma cells using polyethylene glycol and cultured in an HAT medium containing 15% fetal bovine serum, to select only fused cells. At the time when colonies are identified by the naked eye, **calgranulin** antibody-producing cells are confirmed by the ELISA method in which the **calgranulin** is combined with a 96 well immuno plate, and cloning is carried out by the limiting dilution method. The cells obtained are cultured and the monoclonal antibody to **calgranulin** produced in the supernatant is collected.

The monoclonal antibody to **calgranulin** is also available from BMA Company.

To obtain a polyclonal antibody to **calgranulin**, 10-100 .mu.g of **calgranulin** is mixed with a complete Freund's adjuvant and subcutaneously administered to a rabbit. After administration several times, once every two weeks, blood is collected to obtain a polyclonal antibody as antiserum.

The **calgranulin** antibody is added to the cells having **granule secretion** capability having permeabilized cell membranes prepared by the above-mentioned method in an amount of 1-100 .mu.g per 1x10.sup5. to 1x10.sup7. cells, for example, and the mixture is incubated at 4-40.degree.C for 1-30 minutes, whereby the **calgranulin** antibody is introduced into the cells.

Microinjection is another method of introducing **calgranulin** antibody into cell lines, wherein 0.01-10 .mu.g of the **calgranulin** antibody is introduced into the cells by microinjection using an injection needle set in a manipulator under pressure by an injector.

Still another method comprises enclosing 1-100 .mu.g of the **calgranulin** antibody into the above-mentioned liposome, adding the liposome to the cells at a concentration of 0.01-100 .mu.M, preferably 0.1-10 .mu.M, per 1x10.sup5. to 1x10.sup7. cells, and incubating the mixture at 4-40.degree.C for 1-30 minutes.

A **calgranulin** anti-sense gene can be obtained by inserting a gene having a base sequence complementary to the base sequence shown by Sequence ID No. 1 or No. 2, for example. In the present invention, a plasmid vector or virus vector is prepared by insertingl-200 .mu.g of this **calgranulin** anti-sense gene per 0.5x10.sup7. to 3x10.sup7. cells. The resulting vector is incubated at 4-40.degree.C for 5-120 minutes with the addition of 1-100 .mu.g of calcium phosphate, 0.1-10 mg of DEAE dextran, or 1-100 .mu.g of lipofectin. Alternatively, a plasmid vector or virus vector with 1-200 .mu.g of the **calgranulin** anti-sense gene inserted per 0.5x10.sup7. to 3x10.sup7. cells is added and treated by a short electric pulse at 0.05-0.5 kV at a temperature of 4-40.degree.C for 1-30 minutes.

In this manner, an anti-sense gene for a **calgranulin** gene is introduced into a cell line having **granule secretion** capability and knocked out.

A treatment of increasing or decreasing an active form of **calgranulin** in cell lines having **granule secretion** capability can be carried out according to the above-described procedure. As a result, **granule secretion** of a cell line can be controlled by increasing or decreasing **granule secretion** of the cell line.

Granule secretion of neutrophils is known to injure intima of blood vessels as mentioned above. Injury of blood vessel intima is known to be deeply associated with diseases such as adult respiratory distress syndrome (ARDS), injury by reperfusion after

ischemia during acute myocardial infarction, glomerular nephritis, cystic fibrosis, rheumatoid arthritis, chronic bronchitis, cerebral vasospasm, asthma, peripheral circulation disorder, angina pectoris, hypertension, arteriosclerosis,and the like. Therefore, a curative agent, improving agent, or improving method may be provided when **granule secretion** is decreased in the above method for controlling secretion of **granule**. A gene therapy for diseases and phenomenon associated with secretion of neutrophil **granules** , such as adult respiratory distress syndrome (ARDS), injury by reperfusion after ischemia during acute myocardial infarction, glomerular nephritis, cystic fibrosis, rheumatoid arthritis, chronic bronchitis, cerebral spasm, asthma, peripheral circulation disorder, angina pectoris, hypertension, arteriosclerosis, and the like, maybe possible if an anti-sense gene for a **calgranulin** gene is recombined in virus vector introducing the resultant recombinant gene into neutrophils removed from a patient and returning the cells to the patient. Specifically, the above-described **granule secretion** control method includes a curative method and improving method of the above diseases.

The present invention also provides a method of detecting a substance which inhibits or activates the **granule secretion** reaction.

Specifically, the present invention provides a method of detecting a substance which inhibits or activates the **granule secretion** reaction comprising the following steps:

A) A step of increasing an active form of **calgranulin** in cell lines having **granule secretion** capability;

B) A stepof causing a sample which may contain a substance inhibiting or activating the **granule secretion** reaction (hereinafter simply referred to as "sample") to contact with the cell lines having **granule secretion** capability, and incubating the mixture; and

C) A step of detecting the subject substance secreted from the cell line.

The step B) for causing the sample to contact with the cell lines having **granule secretion** capability may be carried out before, after, or during the step A) for increasing an active form of **calgranulin**.

The method of detecting a substance which inhibits or activates the **granule secretion** reaction of the present invention includes a method of quantitative determination of the substance or a method of screening the substance.

The same procedure as described above can be employed in the method of conducting the step A) to increase active form of **calgranulin** of cell lines having **granule secretion** capability. Specifically, the following methods can be given:

a) A method of converting cell membranes of cell lines having **granule secretion** capability, preferably neutrophils or neutrophil-like cultured cells, into permeabilized cell membranes, and simultaneously or successively adding a **calgranulin** and a water-soluble calcium compound.

b) A method of simultaneously or successively adding a **calgranulin** and a water-soluble calcium compound to a cell line having **granule secretion** capability by microinjection using a very fine injection needle.

c) A method of mixing a **calgranulin** and a water-soluble calcium compound, enclosing the mixture in a liposome, and causing the mixture to come into contact with a cell line having **granule secretion** capability to fuse cell membranes.

d) A method of introducing a **calgranulin** gene into a cell line having **granule secretion** capability to cause

the **calgranulin** to be over-expressed and adding a water-soluble calcium compound to the expressed **calgranulin**.

In the step B) of causing a sample which may contain a substance inhibiting or activating the **granule secretion** reaction to contact with the cell lines having **granule secretion** capability, and incubating the mixture, biological components, naturally occurring substances, compounds, and the like can be given as examples of the sample. This procedure of causing the sample to contact with the cell lines having **granule secretion** capability is carried out before, after, or during the step A) of increasing an active form of **calgranulin**. As the cell lines having **granule secretion** capability, the said cell line having **granule secretion** capability itself, a cell line in which the **calgranulin** has been increased, a cell line in which the active form of **calgranulin** has been increased, and the like can be used. The former two cell lines increase an active form of **calgranulin** by the above-mentioned treatment for increasing the active form of **calgranulin**.

In a preferable method of increasing an active form of **calgranulin**, the **calgranulin** is first increased in the cell line having **granule secretion** capability and then a water-soluble calcium compound is increased in this cell line, or an active form of **calgranulin** produced by reacting a **calgranulin** with a water-soluble calcium compound is increased in the cell line having **granule secretion** capability. This sample is caused to contact with the cell line before, after, or during the procedure of increasing the **calgranulin** or active form of **calgranulin**. The procedure of contacting the sample with the cell line is preferable as a method of screening pharmaceutical agents without a treatment in which the sample is penetrated through cell membranes.

A specific example is as follows. In the case where permeabilized cell membranes are used, an appropriate concentration of the sample which may contain a substance inhibiting or activating the **granule secretion** reaction is added to the cell suspension and the mixture is incubated. In this instance, 1-100 .mu.M of the sample is added to a suspension of neutrophils or neutrophil-like cultured cells having permeabilized cell membranes, and the mixture is incubated at 4-40.degree.C for 1-30 minutes. Next, a **calgranulin** is added, and after a while, a water-soluble calcium compound is added. For example, the water-soluble calcium compound is added 1-60 minutes, and preferably 3-10 minutes, after the addition of **calgranulin**. In this instance, the **calgranulin** and water-soluble calcium compound are added in the amount of about 0.01-10 .mu.M each and preferably 0.1-3 .mu.M each. The order of the addition may be either first **calgranulin** and then water-soluble calcium compound, or first the water-soluble calcium compound and then the **calgranulin**. The most preferable method is first preparing an active form of **calgranulin** by the reaction of a **calgranulin** and a water-soluble calcium compound, then adding the active form of **calgranulin** into the above mentioned cell line. The sample may be added to the cell line not only before the addition of the **calgranulin**, but also simultaneously or after the addition of the **calgranulin** or active form of **calgranulin**. The reaction for **granule secretion** is initiated in this manner.

In the case where cells having **granule secretion** capability, for example, neutrophils or neutrophil-like cultured cells are injected by microinjection, an appropriate concentration, for example, 1-100 .mu.M, of the sample which may contain a substance inhibiting or activating the **granule secretion** reaction is added to the neutrophils or neutrophil-like cultured cells,

and the mixture is incubated at 4-40.degree.C for 1-30 minutes. A **calgranulin** is microinjected at an appropriate concentration, for example, at 0.01-10 .mu.M, and preferably 0.1-3 .mu.M, and a water-soluble calcium compound is microinjected simultaneously at a concentration, for example, at 0.01-10 .mu.M, and preferably 0.1-3 .mu.M. Alternatively, the water-soluble calcium compound is microinjected after microinjection of **calgranulin**, for example after 1-60 minutes, preferably after 3-10 minutes, whereby the **granule secretion** reaction is initiated.

In the case where neutrophils or neutrophil-like cultured cells are reacted with a liposome, a sample which may contain a substance inhibiting or activating the **granule secretion** reaction is added to the suspension of the neutrophils or neutrophil-like cultured cells at an appropriate concentration, 1-100 .mu.M, for example, and the mixture is incubated for 1-30 minutes. A **calgranulin** is previously mixed with a water-soluble calcium compound at a concentration of, for example, 0.01-10 .mu.M, and preferably 0.1-3 .mu.M, and the mixture is incubated, for example, at 4-40.degree.C for 1-30 minutes, then introduced into a liposome at a concentration of 0.01-10 .mu.M, and preferably 0.1-3 .mu.M. The liposome is added into a suspension of neutrophils or neutrophil-like cultured cells to initiate the **granule secretion** reaction.

In the case of using cells in which the **calgranulin** is over-expressed, for example neutrophils or neutrophil-like cultured cells into which a **calgranulin** gene has been introduced, an appropriate concentration of sample which may contain a substance inhibiting or activating the **granule secretion** reaction is incubated for 1-30 minutes, for example. A water-soluble calcium compound is added at a concentration of, for example, 0.01-10 .mu.M, and preferably 0.1-3 .mu.M, and the mixture is incubated for 1-30 minutes, for example. Then calcium ionophore, for example, A23187 or ionomycin, is added at a concentration of 0.01-10 .mu.M, and preferably 0.1-3 .mu.M to initiate the **granule secretion** reaction.

Next, the step C) for detecting the subject substance secreted from the cell line is carried out.

Azurophil **granules** (primary **granules**) , specific **granules** (secondary **granules**) , and storage **granules** (tertiary **granules**) are given as **granules** contained in neutrophils. Acidic .beta. -glycerophosphatase, .beta.-glucuronidase, N-acetyl-.beta. -glucurosaminidase, .alpha.- mannosidase, arylsulfatase, .beta. -galactosidase, .alpha.-fucosidase, cathepsin B, cathepsin D, cathepsin G, elastase, proteinase 3, myeloperoxidase, lysozyme, and the like are secreted from Azurophil **granules**. Collagenase, lysozyme, lactoferrin, vitamin B.sub12.-binding protein, cytochrome b, and the like are secreted from the special **granules**. Gelatinase, N-acetyl-.beta.-glucurosaminidase, cathepsin B, cathepsin D,.beta.-glucuronidase, .beta.-glycerophosphatase, -mannosidase, and the like are secreted from storage **granules**. These substances can be selected as a subject substance to be detected. Each of the subject substances can be quantitatively analyzed by means of an appropriate method.

For example, the quantity of myeloperoxidase secreted from Azurophil **granules** can be determined from the rate of increase in the absorbance at 650 nm by a spectrophotometer using 3,3',5,5'-tetramethylbenzidine and a hydrogen peroxide as substrates. Lactoferrin secreted from specific **granules** can be determined by ELISA (enzyme-linked immunoassay, an assay kit manufactured by Oxis Co.) using an antilactoferrin antibody. The quantity of N-acetyl-.beta.-glucurosaminidase, .beta. -glucuronidase, and .alpha.-mannosidase

secreted from storage **granules** can be determined by measuring 4-methylunberiferil which is produced by the hydrolysisof a 4-methylunberiferil derivative (Sigma Co.) as a substrate using fluorescence spectrophotometer at an excitation wavelength of 365 nm and a fluorescence wavelength 450 nm.

The method of detection of a substance which may inhibit or activate the **granule secretion** reaction according to the present invention can be carried out in this manner. Therefore, a substance which inhibits or activates the **granule secretion** reaction contained in the above-mentioned sample can be quantitatively determined.

A preferable example of the quantitative determination of the present invention is as follows.

The target substance (sample) which is an object of screening is caused to be present at an appropriate concentration in a suspension of neutrophils or neutrophil-like cultured cells having permeabilized cell membranes, and a **calgranulin** and a water-soluble calcium compound are added to make an appropriate concentration, respectively, to measure the amount of secreted **granules**. For example, 5x10.sup6. cells/ml to 5x10.sup7. cells/ml of human neutrophils which are treated with digitonin to make the membrane permeabilized membranes is prepared. A sample is added to a concentration of 1-100 .mu.M, followed by the addition of **calgranulin** A (0.01-10 .mu.M, preferably 0.1-3 .mu.M) and an aqueous solution of calcium chloride compound (0.01-10 .mu.M, preferably 0.1-3 .mu.M). The mixture is incubated at 25-40.degree.C, preferably 30-70.degree.C, for 1-60 minutes, and preferably for 5-15 minutes. As examples of the medium used in this incubation buffer solution (pH:about 7-7.4) containing, 100 mM - 200 mM potassium chloride, 10 mM - 20 mM sodium chloride, and 0.3 mM - 3 mM EGTA, for example, phosphoric acid, MOPS, HEPES, Tris, TAPA, BES, and TES buffer containing them can be given. The amount of the substance secreted during the incubation is determined and compared with a control to which no sample is added.

According to the present invention a method of screening a **calgranulin** activity activator, which is used for increasing **calgranulin** activity of neutrophils or neutrophil-like cultured cells and then increasing **granule secretion**, can be provided. Specifically, a substance (sample) which is an object of the screening is selected and caused to be present in a suspension of neutrophils or neutrophil-like cultured cells having permeabilized cell membranes at an appropriate concentration (1-100 .mu.M, for example). A water-soluble calcium compound at an appropriate concentration (for example, 0.01-10 .mu.M, and preferably 0.1-3 .mu.M) and a **calgranulin**, for example **calgranulin** A, at an appropriate concentration (for example, 0.01-10 .mu.M, and preferably 0.1-3 .mu.M) are added to the suspension, thereby screening the substance which increases the quantity of **granules secretion** even more.

A simple method of screening a **calgranulin** activity deactivator can be provided by the method of activating the activity of **calgranulin** permeable through cell membranes of neutrophils or neutrophil-like cultured cells of the present invention. Specifically, a substance (sample) which is an object of screening is selected and caused to be present in a suspension of cultured neutrophils or neutrophil-like cells at an appropriate concentration (1-100 .mu.M, for example). A **calgranulin** activity activator at an appropriate concentration (for example, 0.01-100 .mu.M, and preferably 0.1-10 .mu.M) is added to the suspension, thereby screening the substance which inhibits **granules secretion**.

Granule secretion of neutrophils is known to injure

intima of blood vessels as mentioned above. Injury of blood vessel intima is known to be deeply associated with diseases such as adult respiratory distress syndrome (ARDS), injury by reperfusion after ischemia during acute myocardial infarction, glomerular nephritis, cystic fibrosis, rheumatoid arthritis, chronic bronchitis, cerebral vasospasm, asthma, peripheral circulation disorder, angina pectoris, hypertension, arteriosclerosis, and the like. Therefore, the above method of screening the neutrophil **granule secretion** inhibitor can be applied to the screening of a substance which inhibits the intimal injury of blood vessels.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an elastase secretion reaction of human neutrophils having high permeability cell membranes by **calgranulin** A in Example 1.

Figure 2 shows an elastase secretion reaction of human neutrophils having high permeability cell membranes by **calgranulin** B in Example 1.

Figure 3 shows an elastase secretion reaction of human neutrophils having high permeability cell membranes by a mixture of **calgranulin** A and **calgranulin** B in Example 1.

Figure 4 shows a lactoferrin secretion reaction of human neutrophils having high permeability cell membranes by **calgranulin** A in Example 2.

Figure 5 shows a lactoferrin secretion reaction of human neutrophils having high permeability cell membranes by **calgranulin** B in Example 2.

Figure 6 shows a lactoferrin secretion reaction of human neutrophils having high permeability cell membranes by a mixture of **calgranulin** A and **calgranulin** B in Example 2.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention will now describedmore specifically by way of examples. However, the present invention is not limited to these following examples.

Example 1

<Method of controlling elastase secretion from human neutrophils according to an increase or decrease of **calgranulin** content>

Elastase is a typical secretion substance which is present in primary **granules** of neutrophils. Elastase is a proteinase which decomposes elastin, an elastic protein present in blood vessels, etc., and causes hindrance to occur. A method of controlling elastase secretion by **calgranulin** using human neutrophils will be described.

A neutrophil suspension was prepared from blood collected from human vein according to the method described in Biological Chemistry Experiment Lecture, second series, No. 8, Blood, Vol. 2, 679-685). The neutrophil suspension was adjusted to a concentration of 1x10.sup7. cells/ml in a plastic test tube using a permeabilized buffer (PB) (30 mM HEPES, 100 mM KCl, 20 mM NaCl, 1 mM EGTA, pH 7.0) and incubated at 37.degree.C for 10 minutes. Digitonin (Sigma company) was added to the neutrophil suspension to a final concentration of 5-7.5 .mu.g/ml and the mixture was incubated at 37.degree.C for 15 minutes. The neutrophil suspension was centrifuged at 1200 rpm for 5 minutes. After discarding supernatant, precipitated neutrophils were re-suspended in PB to prepare

a permeabilized neutrophil suspension (cell concentration: 1x10.sup7./ml).

The permeabilized neutrophil suspension was added to a 96-well immunoplate, 200 .mu.l per well, and incubated for at 37.degree.C 15 minutes. Next, an aqueous solution of calcium chloride (final concentration: 1 .mu.M) and **calgranulin** A, **calgranulin** B, or a equimolar mixture of **calgranulin** A and **calgranulin** B (each to a final concentration of 0 .mu.M, 0.3 .mu.M, 1 .mu.M, or 3 .mu.M) were added, and the resulting mixture was incubated at 37.degree.C for 5 minutes.

The 96-well immunoplate was centrifuged at 1200 rpm for one minute at 4.degree.C using a centrifugation container for immunoplates. The supernatant is transferred to another 96-well immunoplate, 160 .mu.l per well, and incubated at 37.degree.C for 5 minutes. 10 mM of an elastase substrate (Suc-Ala-Pro-Ala-pNA, Peptide Laboratory, Inc.) was added to the 96-well immunoplate. After gently shaking, the mixture was incubated at 37.degree.C for 30 minutes. Then, absorbance at 405 nm was measured using a microplate reader.

The results are shown in Figure 1 (**calgranulin** A) , Figure 2 (**calgranulin** B) , and Figure 3 (a mixture of **calgranulin** A and **calgranulin** B). **Calgranulin** A increased elastase secretion from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 1). Assuming that the amount of elastase secretion in the absence of **calgranulin** A is 1, 3 .mu.M of **calgranulin** A remarkably increased the amount of elastase secretion (about eight times).

Calgranulin B increased elastase secretion from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 2). Assuming that the amount of elastase secretion in the absence of **calgranulin** B is 1, 3 .mu.M of **calgranulin** B remarkably increased the amount of elastase secretion (about seven times). A mixture of **calgranulin** A and **calgranulin** B increased elastase secretion from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 3). Assuming that the amount of elastase secretion in the absence of the mixture is 1, 3 .mu.M of the mixture of **calgranulin** A and **calgranulin** B remarkably increased the amount of elastase secretion (about six times).

These results show that change in the amount of **calgranulin** A, **calgranulin** B, or a mixture of **calgranulin** A and **calgranulin** B in neutrophils can remarkably change the amount of elastase secretion.

Example 2

<Method of controlling lactoferrin secretion from human neutrophils according to an increase or decrease of **calgranulin** content>

Lactoferrin is a typical secretion substance which is present in secondary **granules** of neutrophils. A method of controlling lactoferrin secretion by **calgranulin** using human neutrophils will be described.

A neutrophil suspension was prepared from blood collected from human vein according to the method described in Biological Chemistry Experiment Lecture, second series, No. 8, Blood, Vol. 2, 679-685). The neutrophil suspension was adjusted to a concentration of 1x10.sup7. cells/ml using PB in a plastic test tube and incubated at 37.degree.C for 10 minutes. Digitonin (Sigma company) was added to the neutrophil suspension to a final concentration of 5 .mu.g/ml and the mixture was

incubated at 37.degree.C for 15 minutes.

The neutrophil suspension was centrifuged at 1200 rpm for 5 minutes. After supernatant was discarded, precipitated neutrophils were re-suspended in PB to prepare a permeabilized neutrophil suspension (cell concentration: 1x10.sup7. cells/ml). The permeabilized neutrophil suspension was added to a 96-well immunoplate, 200 .mu.l per well, and incubated at 37.degree.C for 15 minutes. Next, an aqueous solution of calcium chloride (final concentration: 1 .mu.M) and **calgranulin** A, **calgranulin** B, or a equimolar mixture of **calgranulin** A and **calgranulin** B (each to a final concentration of 0 .mu.M, 0.3 .mu.M, 1 .mu.M, or 3 .mu.M) were added, and the resulting mixtures were incubated at 37.degree.C for 5 minutes. The 96-well immunoplate was centrifuged at 1200 rpm for one minute at 4.degree.C. ELISA-kit (OXIS Co.) was used for the determination of lactoferrin. The results are shown in Figures 4, 5, and 6. **Calgranulin** A increased lactoferrin secretion from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 4). Assuming that the amount of lactoferrin secretion in the absence of **calgranulin** A is 1, 3 .mu.M of **calgranulin** A remarkably increased the amount of lactoferrin secretion (about six times) . **Calgranulin** B increased lactoferrin secretion from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 5). Assuming that the amount of lactoferrin secretion in the absence of **calgranulin** B is 1, 3 .mu.M of **calgranulin** B remarkably increased the amount of lactoferrin secretion (about five times) . Amixture of **calgranulin** A and **calgranulin** B increased lactoferrin secretion from neutrophils if the amount of addition is increased to increase the **calgranulin** activity (Figure 6) . Assuming that the amount of lactoferrin secretion in the absence of the mixture is 1, 3 .mu.M of the mixture of **calgranulin** A and **calgranulin** B remarkably increased the amount of lactoferrin secretion (about five times).

These results show that change in the amount of **calgranulin** A, **calgranulin** B, or a mixture of **calgranulin** A and **calgranulin** B in neutrophils can remarkably change the amount of lactoferrin secretion.

The results of Examples 1 and 2 show that **calgranulins** are important proteins to control **granule secretion** form neutrophils.

Example 3

<Method of Screening a substance inhibiting or activating **granule secretion** by allowing a sample to stand in the system in which the amount of elastase secretion from neutrophils is greatly increased by changing **calgranulin** activity>

A neutrophil suspension was prepared from blood collected from a human vein according to the method described in Biological Chemistry Experiment Lecture, second series, No. 8, Blood, Vol. 2, 679-685). The neutrophil suspension was adjusted to a concentration of 1x10.sup7. cells/ml using PB in a plastic test tube and incubated at 37.degree.C for 10 minutes. Digitonin was added to the neutrophil suspension to a final concentration of 5 .mu.g/ml and the mixture was incubated at 37.degree.C for 15 minutes. The neutrophil suspension was centrifuged at 1200 rpm for 5 minutes.

After supernatant was discarded, the precipitate was re-suspended in PB to prepare a permeabilized neutrophil suspension (cell concentration: 1x10.sup7. cells/ml). The permeabilized neutrophil suspension was added to a 96-well immunoplate, 200 .mu.l per well, and incubated at 37.degree.C for 15 minutes. N-(4-methoxybenzyl)-N-(4-methoxyphenyl)-7-

piperazinylheptyl amine trihydrochloride (Compound 1), N-benzyl-N-(4-methoxyphenyl)-7-piperazinylheptylamine trihydrochloride (Compound 2), 1,1-(di-4-hydroxyphenyl)-2-ethyl-1-octaene (Compound 3), and 2-hydroxy-5-((-4-((-2-pyridinylamino)sulfonyl)phenyl)azo)be nzoic acid (Compound 4) were used as samples for screening.

These samples were added to a final concentration of 30 .mu.M and the mixtures were incubated at 37.degree.C for 15 minutes. Next, an aqueous solution of calcium chloride (final concentration: 1 .mu.M) and **calgranulin** A, **calgranulin** B, or a equimolar mixture of **calgranulin** A and **calgranulin** B (each to a final concentration of 0 .mu.M, 0.3 .mu.M, 1 .mu.M, or 3 .mu.M) were added, and the resulting mixtures were incubated at 37.degree.C for 5 minutes. The 96-well immunoplate was centrifuged at 1200 rpm for one minute at 4.degree.C using a centrifugal separator for immunoplates. The supernatant is transferred to another 96-well immunoplate and incubated at 37.degree.C for 5 minutes. 10 mM of an elastase substrate (Suc-Ala-Pro-Ala-pNA) was added to the 96-well immunoplate. After gently shaking, the mixture was incubated at 37.degree.C for 30 minutes. Then, absorbance at 405 nm was measured using a microplate reader.

The results are shown in Table 1. The secretion inhibiting rate of samples was determined by comparison with a control which does not contain the screening sample, assuming that the secretion from the control is 100%. Compound 1 and Compound 2 increased the activity of **calgranulin** A and remarkably controlled **granule secretion** in a system in which the amount of elastase secretion from neutrophils has been remarkably increased. Compound 3 remarkably increased the amount of secretion in the above system. <table>

INDUSTRIAL APPLICABILITY

<image> <image> <image> <image>

CLMEN 1. A method of controlling **granule secretion** comprising performing a treatment to increase or decrease an active form of **calgranulin** on a cell line having **granules secretion** capability, thereby increasing or decreasing **granule secretion** from the cell line.

2. The method according to claim 1, wherein the cell line having **granule secretion** capability is neutrophils or neutrophil-like cultured cells originating from a warm-blooded animal.

3. The method according to claim 1 or claim 2, wherein the active form of **calgranulin** is one or more of the following peptides:

(i) A peptide consisting of the amino acid sequence 1-93 of Sequence ID No. 1 of the Sequence Table and binding calcium thereto,

(ii) A peptide consisting of the amino acid sequence 1-114 of Sequence ID No. 2 of the Sequence Table and binding calcium thereto, and

(iii) A peptide having an amino acid sequence in which one or more amino acids are deleted from or added to the amino acid sequence of Sequence ID No. 1 or 2 of the Sequence Table, or one or more amino acids in the amino acid sequence of Sequence ID No. 1 or 2 are replaced with other amino acids, binding calcium thereto, and exhibiting the activity of increasing secretion of **granules** of cell lines having **granule secretion** capability.

4. A method of detecting a substance which inhibits or activates a **granule secretion** reaction comprising the following steps:

A) a step of increasing an active form of **calgranulin** in cell lines having **granule secretion** capability;

B) a step of causing a sample which may contain a substance inhibiting or activating the **granule secretion** reaction to contact with the cell lines having **granule**

secretion capability before, after, or during the step A) , and incubating the mixture; and

C) a step of detecting the subject substance secreted from the cell line.

5. A method according to claim 4, wherein the step A) of increasing an active form of **calgranulin** in a cell line having the capability of secreting **granules** comprises successively carrying out the following steps a) and b):

a) a step of changing the cell line having **granule secretion** capability into a permeabilized cell; and

b) a step of simultaneously or successively adding a **calgranulin** and a water-soluble calcium compound to the cell line and incubating the cell line.

6. The method according to claim 4 or claim 5, wherein the cell line having **granule secretion** capability is neutrophils originating from a warm-blooded animal or neutrophil-like cultured cells.

7. The method according to any one of claims 4-6, wherein the active form of **calgranulin** is one or more of the following peptides:

(i) A peptide consisting of the amino acid sequence 1-93 of Sequence ID No. 1 of the Sequence Table and binding calcium thereto,

(ii) A peptide consisting of the amino acid sequence 1-114 of Sequence ID No. 2 of the Sequence Table and binding calcium thereto, and

(iii) A peptide having an amino acid sequence in which one or more amino acids are deleted from or added to the amino acid sequence of Sequence ID No. 1 or 2 of the Sequence Table, or one or more amino acids in the amino acid sequence of Sequence ID No. 1 or 2 are replaced with other amino acids, binding calcium thereto, and exhibiting the activity of increasing secretion of **granules** of cell lines having **granule secretion** capability.

8. The method according to claim 5, wherein the water-soluble calcium compound is a solution or powder of a compound which produces calcium ions at a concentration of 100 mM or more when the compound contacts with water.

9. The method according to any one of claims 4-8, wherein the method of detection is a quantitative determination method.

10. The method according to any one of claims 4-8, wherein the method of detection is a screening method.

11. A method of obtaining a substance for controlling intimal injury of blood vessels comprising acquiring the substance for controlling intimal injury of blood vessels by screening a substance inhibiting **granule secretion** reaction by the method of claim 10.

L18 ANSWER 2 OF 2 PATOSEP COPYRIGHT 2002 WILA

PATENT APPLICATION

AN 1999:387200 PATOSEP ED 20010802 EW 200130 FS OS
TIEN METHOD FOR CONTROLLING THE RELEASE OF **GRANULES**.
IN SETO, Minoru, 572-33, Mitsuzawa, Fuji-shi, Sizuoka 417-0855, JP; FUKUDA, Kouichirou, 282-1, Yunoki, Fuji-shi, Sizuoka 416-0908, JP
PA Asahi Kasei Kabushiki Kaisha, 2-6, Dojimahama 1-chome, Kita-ku, Osaka-shi, Osaka 530-8205, JP
PAN 219576
AG Forstmeyer, Dietmar, Dr. rer. nat., Dipl.-Chem. et al., Boeters & Bauer, Bereiteranger 15, 81541 Muenchen, DE
AGN 77023
OS BEPA2001058 EP 1118681 A1 0021

SO Wila-EPZ-2001-H30-T1a
DT Patent
LA Anmeldung in Japanisch; Veroeffentlichung in Englisch;
Verfahren in Englisch
DS R AT; R BE; R CH; R CY; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE;
R IT; R LI; R LU; R MC; R NL; R PT; R SE
PIT EPA1 EUROPAEISCHE PATENTANMELDUNG (Internationale Anmeldung)
PI EP 1118681 A1 20010725
OD 20010725
AI EP 1999-944877 19990928
PRAI JP 1998-274574 19980929
RLI WO 99-JP5302 990928 INTAKZ
WO 0018970 000406 INTPNR
IC ICM C12Q003-00
ICS C07K014-47 C12Q001-02
MCLMEN 1. A method of controlling **granule secretion**
comprising performing a treatment to increase or decrease an active form
of **calgranulin** on a cell line having **granules**
secretion capability, thereby increasing or decreasing
granule secretion from the cell line.
ABEN The present invention is a very useful method of controlling
granule secretion from neutrophils. The detecting
method, screening method, or quantitative determination method of
substances inhibiting or activating **granule secretion**
based on the above method is very useful in providing therapeutic drugs
for various diseases due to intimal injury of blood vessels brought
about by **granules secretion** of neutrophil.
FA I1; PRAI; ICS; AG; INA; PAA; AGA; AGN; PAN; RLI; MCLMEN; ABEN

LEGAL STATUS

AN 1999:387200 PATOSEP ED 20010802 EW 200130 FS RS
SO EP-PB-2001-H30
DT Historie
PIT EPLU LEGAL STATUS, UPDATE
PI EP 1118681 AL 20010725
LSEN EP-Bul Code Text
010725 AD Application date 990928
010725 OD Laid open date (publication) of A-Doc.
010725 EX-RQ Examination requested 010427
FA LS

=>

WEST Search History

DATE: Tuesday, October 01, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,EPAB,DWPI,TDBD; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L5	calgranulin and (granule adj secretion or secretion adj of adj granule)	0	L5
L4	calgranulin and neutrophil	13	L4
L3	calgranulin and (granule adj secretion)	0	L3
L2	L1 and secretion	8	L2
L1	calgranulin and (calcium adj binding)	17	L1

END OF SEARCH HISTORY

WEST

Generate Collection | Print

Search Results - Record(s) 1 through 13 of 13 returned.

☐ 1. Document ID: US 20020122799 A1

L4: Entry 1 of 13 File: PGPB Sep 5, 2002

PGPUB-DOCUMENT-NUMBER: 20020122799
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020122799 A1

TITLE: Methods for treating inflammation

PUBLICATION-DATE: September 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Stern, David M.	Great Neck	NY	US	
Herold, Kevan	Scarsdale	NY	US	
Yan, Shi Du	Tenafly	NJ	US	
Schmidt, Ann Marie	Franklin Lakes	NJ	US	
Lamster, Ira	Wycoff	NJ	US	

US-CL-CURRENT: 424/143.1; 514/12, 514/23, 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20020106726 A1

L4: Entry 2 of 13 File: PGPB Aug 8, 2002

PGPUB-DOCUMENT-NUMBER: 20020106726
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020106726 A1

TITLE: Extracellular novel RAGE binding protein (EN-RAGE) and uses thereof

PUBLICATION-DATE: August 8, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Schmidt, Ann Marie	Franklin Lakes	NJ	US	
Stern, David	Great Neck	NY	US	

US-CL-CURRENT: 435/69.1; 435/320.1, 435/325, 530/350, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 20020037538 A1

L4: Entry 3 of 13 File: PGPB Mar 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020037538
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020037538 A1

TITLE: Compositions, kits, and methods for identification, assessment, prevention, and therapy of psoriasis

PUBLICATION-DATE: March 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Trepicchio, William L.	Andover	MA	US	
Oestreicher, Judith L.	Portsmouth	NH	US	
Dorner, Andrew J.	Lexington	MA	US	
Krueger, James G.	New York	NY	US	

US-CL-CURRENT: 435/7.21; 435/6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 20020009730 A1

L4: Entry 4 of 13 File: PGPB Jan 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020009730
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020009730 A1

TITLE: Human stress array

PUBLICATION-DATE: January 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Chenchik, Alex	Palo Alto	CA	US	
Lukashev, Matvey E.	Newton	MA	US	

US-CL-CURRENT: 435/6; 536/24.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 6228983 B1

L4: Entry 5 of 13 File: USPT May 8, 2001

US-PAT-NO: 6228983
DOCUMENT-IDENTIFIER: US 6228983 B1

TITLE: Human respiratory syncytial virus peptides with antifusogenic and antiviral activities

DATE-ISSUED: May 8, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 530/300; 424/186.1, 424/211.1, 530/324, 530/325, 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 6218128 B1

L4: Entry 6 of 13 File: USPT Apr 17, 2001

US-PAT-NO: 6218128
DOCUMENT-IDENTIFIER: US 6218128 B1

TITLE: Methods of identifying compounds having nuclear receptor negative hormone and/or antagonist activities

DATE-ISSUED: April 17, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliott S.	Marina Del Rey	CA		
Nagpal; Sunil	Lake Forest	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 7. Document ID: US 6093794 A

L4: Entry 7 of 13 File: USPT Jul 25, 2000

US-PAT-NO: 6093794
DOCUMENT-IDENTIFIER: US 6093794 A

TITLE: Isolated peptides derived from the Epstein-Barr virus containing fusion inhibitory domains

DATE-ISSUED: July 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 530/300; 424/186.1, 424/230.1, 530/324, 530/325, 530/326, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 8. Document ID: US 6068973 A

L4: Entry 8 of 13 File: USPT May 30, 2000

US-PAT-NO: 6068973
DOCUMENT-IDENTIFIER: US 6068973 A

TITLE: Methods for inhibition of membrane fusion-associated events, including influenza virus

DATE-ISSUED: May 30, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 435/5; 424/147.1, 424/206.1, 424/230.1, 530/324, 530/389.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 9. Document ID: US 6060065 A

L4: Entry 9 of 13 File: USPT May 9, 2000

US-PAT-NO: 6060065
DOCUMENT-IDENTIFIER: US 6060065 A

TITLE: Compositions for inhibition of membrane fusion-associated events, including influenza virus transmission

DATE-ISSUED: May 9, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 424/209.1; 424/186.1, 424/192.1, 424/206.1, 530/300, 530/324, 530/325, 530/326, 530/327, 530/328, 530/329 , 530/330

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 10. Document ID: US 6054265 A

L4: Entry 10 of 13 File: USPT Apr 25, 2000

US-PAT-NO: 6054265
DOCUMENT-IDENTIFIER: US 6054265 A

TITLE: Screening assays for compounds that inhibit membrane fusion-associated events

DATE-ISSUED: April 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway, Jr.; Stephen Robert	Cary	NC		

US-CL-CURRENT: 435/5; 435/7.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 11. Document ID: US 6017536 A

L4: Entry 11 of 13 File: USPT Jan 25, 2000

US-PAT-NO: 6017536
DOCUMENT-IDENTIFIER: US 6017536 A

TITLE: Simian immunodeficiency virus peptides with antifusogenic and antiviral activities

DATE-ISSUED: January 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		
Langlois; Alphonse J.	Durham	NC		

US-CL-CURRENT: 424/188.1; 424/208.1, 530/300, 530/324, 530/325, 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 12. Document ID: US 6013263 A

L4: Entry 12 of 13 File: USPT Jan 11, 2000

US-PAT-NO: 6013263
DOCUMENT-IDENTIFIER: US 6013263 A

TITLE: Measles virus peptides with antifusogenic and antiviral activities

DATE-ISSUED: January 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 424/212.1; 424/184.1, 424/186.1, 530/300, 530/324, 530/325, 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 13. Document ID: US 5776348 A

L4: Entry 13 of 13 File: USPT Jul 7, 1998

US-PAT-NO: 5776348
DOCUMENT-IDENTIFIER: US 5776348 A

TITLE: Mineral precipitation system and method for inhibiting mineral precipitate formation

DATE-ISSUED: July 7, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Selengut; Jeremy D.	Brookline	MA		
Orme-Johnson; William H.	Cambridge	MA		
Dretler; Stephen P.	Whayland	MA		
Asakura; Hirotaka	Arlington	MA		

US-CL-CURRENT: 210/698; 210/702

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Term	Documents
CALGRANULIN.DWPI,TDBD,EPAB,USPT,PGPB.	21
CALGRANULINS	0
NEUTROPHIL.DWPI,TDBD,EPAB,USPT,PGPB.	6109
NEUTROPHILS.DWPI,TDBD,EPAB,USPT,PGPB.	7982
(CALGRANULIN AND NEUTROPHIL).USPT,PGPB,EPAB,DWPI,TDBD.	13
(CALGRANULIN AND NEUTROPHIL).USPT,PGPB,EPAB,DWPI,TDBD.	13

Display Format: - Change Format

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1: Nature 1987 Nov 5-11;330(6143):80-2 Related Articles, Links

Two calcium-binding proteins in infiltrate macrophages of rheumatoid arthritis.

Odink K, Cerletti N, Bruggen J, Clerc RG, Tarcsay L, Zwadlo G, Gerhards G, Schlegel R, Sorg C.

Department of Biotechnology, Ciba-Geigy, Basel, Switzerland.

The aetiology and cellular mechanism of chronic inflammatory processes are poorly understood. Macrophages act prominently in the inflammatory response and we report here that they express two calcium-binding proteins. The expression of these proteins, referred to as MRP-8 and MRP-14, is specific for cells of myeloid origin, namely granulocytes, monocytes and macrophages, and is observed in blood granulocytes and monocytes but not in normal tissue macrophages. In acutely inflamed tissues, macrophages can express MRP-14 but not MRP-8, and in chronic inflammations, such as primary chronic polyarthritis, infiltrate macrophages express both MRP-8 and MRP-14. Characterization of MRP-8 and MRP-14 could therefore be useful to the understanding of cellular processes induced in chronic inflammation.

PMID: 3313057 [PubMed - indexed for MEDLINE]

WEST Search History

DATE: Wednesday, October 16, 2002

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,EPAB,DWPI,TDBD; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
L5	L4 and (intimal same injury or injure or intima same blood same vessel?)	0	L5
L4	L3 and secretion	10	L4
L3	(calgranulin or mrp-8 or mrp-14)	57	L3
L2	granule adj secretion and (calgranulin or mrp-8 or mrp-14)	0	L2
L1	granule adj secretion	60	L1

END OF SEARCH HISTORY

WEST

Generate Collection | Print

Search Results - Record(s) 1 through 10 of 10 returned.

☐ 1. Document ID: US 20020042366 A1

L4: Entry 1 of 10 File: PGPB Apr 11, 2002

PGPUB-DOCUMENT-NUMBER: 20020042366
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020042366 A1

TITLE: Method for treating inflammation

PUBLICATION-DATE: April 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Thompson, Penny	Snohomish	WA	US	
Foster, Donald C.	Lake Forest Park	WA	US	
Xu, Wenfeng	Mukilteo	WA	US	
Madden, Karen L.	Bellevue	WA	US	
Kelly, James D.	Mercer Island	WA	US	
Sprecher, Cindy A.	Seattle	WA	US	
Blumberg, Hal	Seattle	WA	US	
Eagan, Maribeth A.	Seattle	WA	US	
Jaspers, Stephen R.	Edmonds	WA	US	
Chandrasekher, Yasmin A.	Mercer Island	WA	US	
Novak, Julia E.	Bainbridge Island	WA	US	

US-CL-CURRENT: 514/12; 424/145.1, 424/85.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20020037538 A1

L4: Entry 2 of 10 File: PGPB Mar 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020037538
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020037538 A1

TITLE: Compositions, kits, and methods for identification, assessment, prevention, and therapy of psoriasis

PUBLICATION-DATE: March 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Trepicchio, William L.	Andover	MA	US	
Oestreicher, Judith L.	Portsmouth	NH	US	
Dorner, Andrew J.	Lexington	MA	US	
Krueger, James G.	New York	NY	US	

US-CL-CURRENT: 435/7.21; 435/6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 3. Document ID: US 20020034773 A1

L4: Entry 3 of 10 File: PGPB Mar 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020034773
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020034773 A1

TITLE: S100 proteins and autoantibodies as serum markers for cancer

PUBLICATION-DATE: March 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hanash, Samir M.	Ann Arbor	MI	US	
Misek, David	Ann Arbor	MI	US	
Prasannan, Latha	Marshfield	WI	US	

US-CL-CURRENT: 435/7.23

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 6228983 B1

L4: Entry 4 of 10 File: USPT May 8, 2001

US-PAT-NO: 6228983
DOCUMENT-IDENTIFIER: US 6228983 B1

TITLE: Human respiratory syncytial virus peptides with antifusogenic and antiviral activities

DATE-ISSUED: May 8, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 530/300; 424/186.1, 424/211.1, 530/324, 530/325, 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 6093794 A

L4: Entry 5 of 10 File: USPT Jul 25, 2000

US-PAT-NO: 6093794
DOCUMENT-IDENTIFIER: US 6093794 A

TITLE: Isolated peptides derived from the Epstein-Barr virus containing fusion inhibitory domains

DATE-ISSUED: July 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 530/300; 424/186.1, 424/230.1, 530/324, 530/325, 530/326, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 6. Document ID: US 6068973 A

L4: Entry 6 of 10 File: USPT May 30, 2000

US-PAT-NO: 6068973
DOCUMENT-IDENTIFIER: US 6068973 A

TITLE: Methods for inhibition of membrane fusion-associated events, including influenza virus

DATE-ISSUED: May 30, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 435/5; 424/147.1, 424/206.1, 424/230.1, 530/324, 530/389.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 7. Document ID: US 6060065 A

L4: Entry 7 of 10 File: USPT May 9, 2000

US-PAT-NO: 6060065
DOCUMENT-IDENTIFIER: US 6060065 A

TITLE: Compositions for inhibition of membrane fusion-associated events, including influenza virus transmission

DATE-ISSUED: May 9, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 424/209.1; 424/186.1, 424/192.1, 424/206.1, 530/300, 530/324, 530/325, 530/326, 530/327, 530/328, 530/329 , 530/330

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 8. Document ID: US 6054265 A

L4: Entry 8 of 10 File: USPT Apr 25, 2000

US-PAT-NO: 6054265
DOCUMENT-IDENTIFIER: US 6054265 A

TITLE: Screening assays for compounds that inhibit membrane fusion-associated events

DATE-ISSUED: April 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway, Jr.; Stephen Robert	Cary	NC		

US-CL-CURRENT: 435/5; 435/7.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 9. Document ID: US 6017536 A

L4: Entry 9 of 10 File: USPT Jan 25, 2000

US-PAT-NO: 6017536
DOCUMENT-IDENTIFIER: US 6017536 A

TITLE: Simian immunodeficiency virus peptides with antifusogenic and antiviral activities

DATE-ISSUED: January 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		
Langlois; Alphonse J.	Durham	NC		

US-CL-CURRENT: 424/188.1; 424/208.1, 530/300, 530/324, 530/325, 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 10. Document ID: US 6013263 A

L4: Entry 10 of 10 File: USPT Jan 11, 2000

US-PAT-NO: 6013263
DOCUMENT-IDENTIFIER: US 6013263 A

TITLE: Measles virus peptides with antifusogenic and antiviral activities

DATE-ISSUED: January 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 424/212.1; 424/184.1, 424/186.1, 530/300, 530/324, 530/325, 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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Term	Documents
SECRETION.DWPI,TDBD,EPAB,USPT,PGPB.	40272
SECRETIONS.DWPI,TDBD,EPAB,USPT,PGPB.	8298
(3 AND SECRETION).USPT,PGPB,EPAB,DWPI,TDBD.	10
(L3 AND SECRETION).USPT,PGPB,EPAB,DWPI,TDBD.	10

Display Format: - Change Format

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Search Results - Record(s) 1 through 5 of 5 returned.

☐ 1. Document ID: US 6533060 B1

L1: Entry 1 of 5 File: USPT Mar 18, 2003

US-PAT-NO: 6533060
DOCUMENT-IDENTIFIER: US 6533060 B1

TITLE: ATV transmission

DATE-ISSUED: March 18, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Seto; Minoru	Shizuoka			JP

US-CL-CURRENT: 180/337; 180/215, 180/258, 180/371, 464/178

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6250415 B1

L1: Entry 2 of 5 File: USPT Jun 26, 2001

US-PAT-NO: 6250415
DOCUMENT-IDENTIFIER: US 6250415 B1

TITLE: Atv transmission

DATE-ISSUED: June 26, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Seto; Minoru	Shizuoka			JP

US-CL-CURRENT: 180/337; 180/371, 464/906

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 6076624 A

L1: Entry 3 of 5 File: USPT Jun 20, 2000

US-PAT-NO: 6076624
DOCUMENT-IDENTIFIER: US 6076624 A

TITLE: Drive layout for offroad vehicle

DATE-ISSUED: June 20, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Izumi; Kazuhiko	Iwata			JP
Seto; Minoru	Iwata			JP

US-CL-CURRENT: 180/291

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

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☐ 4. Document ID: EP 1118681 A1

L1: Entry 4 of 5 File: EPAB Jul 25, 2001

PUB-NO: EP001118681A1
DOCUMENT-IDENTIFIER: EP 1118681 A1
TITLE: METHOD FOR CONTROLLING THE RELEASE OF GRANULES

PUBN-DATE: July 25, 2001

INVENTOR-INFORMATION:

NAME	COUNTRY
SETO, MINORU	JP
FUKUDA, KOUICHIROU	JP

INT-CL (IPC): C12 Q 3/00; C07 K 14/47; C12 Q 1/02
EUR-CL (EPC): G01N033/50

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 5. Document ID: WO 9405290 A1

L1: Entry 5 of 5 File: EPAB Mar 17, 1994

PUB-NO: WO009405290A1
DOCUMENT-IDENTIFIER: WO 9405290 A1
TITLE: PLATELET AGGREGATION INHIBITOR

PUBN-DATE: March 17, 1994

INVENTOR-INFORMATION:

NAME	COUNTRY
SETO, MINORU	JP
SATO, TAE	JP

INT-CL (IPC): A61K 31/47; A61K 31/495; A61K 31/55
EUR-CL (EPC): A61K031/47; C07D217/02, C07D217/22 , C07D217/24

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Clip Img | Image

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Term	Documents
SETO-MINORU.DWPI,EPAB,USPT,PGPB.	5
SETO-MINORUS	0
SETO-MINORU.IN..USPT,PGPB,EPAB,DWPI,TDBD.	5
(SETO-MINORU.IN.).USPT,PGPB,EPAB,DWPI,TDBD.	5

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Search Results - Record(s) 1 through 1 of 1 returned.

☐ 1. Document ID: EP 1118681 A1

L2: Entry 1 of 1 File: EPAB Jul 25, 2001

PUB-NO: EP001118681A1
DOCUMENT-IDENTIFIER: EP 1118681 A1
TITLE: METHOD FOR CONTROLLING THE RELEASE OF GRANULES

PUBN-DATE: July 25, 2001

INVENTOR-INFORMATION:

NAME	COUNTRY
SETO, MINORU	JP
FUKUDA, KOUICHIROU	JP

INT-CL (IPC): C12 Q 3/00; C07 K 14/47; C12 Q 1/02
EUR-CL (EPC): G01N033/50

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

Generate Collection | Print

Term	Documents
FUKUDA-KOUICHIROU.DWPI,EPAB,USPT,PGPB.	1
FUKUDA-KOUICHIROUS	0
FUKUDA-KOUICHIROU.IN..USPT,PGPB,EPAB,DWPI,TDBD.	1
(FUKUDA-KOUICHIROU.IN.).USPT,PGPB,EPAB,DWPI,TDBD.	1

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WEST Search History

DATE: Wednesday, April 16, 2003

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L2	fukuda-kouichirou.in.	1	L2
L1	seto-minoru.in.	5	L1

END OF SEARCH HISTORY

WEST Search History

DATE: Wednesday, October 02, 2002

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DB=USPT,PGPB,EPAB,DWPI,TDBD; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L2	L1 and secretion	2	L2
L1	msrp-8 or mrp-14	11	L1

END OF SEARCH HISTORY

WEST

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Search Results - Record(s) 1 through 2 of 2 returned.

☐ 1. Document ID: US 20020042366 A1

L2: Entry 1 of 2 File: PGPB Apr 11, 2002

PGPUB-DOCUMENT-NUMBER: 20020042366
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020042366 A1

TITLE: Method for treating inflammation

PUBLICATION-DATE: April 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Thompson, Penny	Snohomish	WA	US	
Foster, Donald C.	Lake Forest Park	WA	US	
Xu, Wenfeng	Mukilteo	WA	US	
Madden, Karen L.	Bellevue	WA	US	
Kelly, James D.	Mercer Island	WA	US	
Sprecher, Cindy A.	Seattle	WA	US	
Blumberg, Hal	Seattle	WA	US	
Eagan, Maribeth A.	Seattle	WA	US	
Jaspers, Stephen R.	Edmonds	WA	US	
Chandrasekher, Yasmin A.	Mercer Island	WA	US	
Novak, Julia E.	Bainbridge Island	WA	US	

US-CL-CURRENT: 514/12; 424/145.1, 424/85.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20020034773 A1

L2: Entry 2 of 2 File: PGPB Mar 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020034773
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020034773 A1

TITLE: S100 proteins and autoantibodies as serum markers for cancer

PUBLICATION-DATE: March 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hanash, Samir M.	Ann Arbor	MI	US	
Misek, David	Ann Arbor	MI	US	
Prasannan, Latha	Marshfield	WI	US	

US-CL-CURRENT: 435/7.23

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

Generate Collection | Print

Term	Documents
SECRETION.DWPI,TDBD,EPAB,USPT,PGPB.	39838
SECRETIONS.DWPI,TDBD,EPAB,USPT,PGPB.	8224
(1 AND SECRETION).USPT,PGPB,EPAB,DWPI,TDBD.	2
(L1 AND SECRETION).USPT,PGPB,EPAB,DWPI,TDBD.	2

Display Format: - Change Format

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Generate Collection | Print

Search Results - Record(s) 1 through 11 of 11 returned.

☐ 1. Document ID: US 20020106726 A1

L1: Entry 1 of 11 File: PGPB Aug 8, 2002

PGPUB-DOCUMENT-NUMBER: 20020106726
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020106726 A1

TITLE: Extracellular novel RAGE binding protein (EN-RAGE) and uses thereof

PUBLICATION-DATE: August 8, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Schmidt, Ann Marie	Franklin Lakes	NJ	US	
Stern, David	Great Neck	NY	US	

US-CL-CURRENT: 435/69.1; 435/320.1, 435/325, 530/350, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20020090625 A1

L1: Entry 2 of 11 File: PGPB Jul 11, 2002

PGPUB-DOCUMENT-NUMBER: 20020090625
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020090625 A1

TITLE: Methods of detecting cancer based on prostasin

PUBLICATION-DATE: July 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Mok, Samuel C.	Brookline	MA	US	
Wong, Kwong-Kwok	Sugar Land	TX	US	

US-CL-CURRENT: 435/6; 435/7.23, 435/7.92

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 3. Document ID: US 20020042366 A1

L1: Entry 3 of 11 File: PGPB Apr 11, 2002

PGPUB-DOCUMENT-NUMBER: 20020042366
PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020042366 A1

TITLE: Method for treating inflammation

PUBLICATION-DATE: April 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Thompson, Penny	Snohomish	WA	US	
Foster, Donald C.	Lake Forest Park	WA	US	
Xu, Wenfeng	Mukilteo	WA	US	
Madden, Karen L.	Bellevue	WA	US	
Kelly, James D.	Mercer Island	WA	US	
Sprecher, Cindy A.	Seattle	WA	US	
Blumberg, Hal	Seattle	WA	US	
Eagan, Maribeth A.	Seattle	WA	US	
Jaspers, Stephen R.	Edmonds	WA	US	
Chandrasekher, Yasmin A.	Mercer Island	WA	US	
Novak, Julia E.	Bainbridge Island	WA	US	

US-CL-CURRENT: 514/12; 424/145.1, 424/85.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 20020034773 A1

L1: Entry 4 of 11 File: PGPB Mar 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020034773
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020034773 A1

TITLE: S100 proteins and autoantibodies as serum markers for cancer

PUBLICATION-DATE: March 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hanash, Samir M.	Ann Arbor	MI	US	
Misek, David	Ann Arbor	MI	US	
Prasannan, Latha	Marshfield	WI	US	

US-CL-CURRENT: 435/7.23

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 20010036631 A1

L1: Entry 5 of 11 File: PGPB Nov 1, 2001

PGPUB-DOCUMENT-NUMBER: 20010036631
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010036631 A1

TITLE: Evaluating and predicting clinical outcomes by gene expression analysis

PUBLICATION-DATE: November 1, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
McGrath, Michael	Burlingame	CA	US	
Meuer, Stefan	Heldelberg		DE	
Kuehne, Friedrich-Wilhelm	Bangkok		TH	

US-CL-CURRENT: 435/6; 435/5, 435/91.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 5994076 A

L1: Entry 6 of 11 File: USPT Nov 30, 1999

US-PAT-NO: 5994076
DOCUMENT-IDENTIFIER: US 5994076 A

TITLE: Methods of assaying differential expression

DATE-ISSUED: November 30, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chenchik; Alex	Palo Alto	CA		
Jokhadze; George	Mountain View	CA		
Bibilashvilli; Robert	Moscow			RU

US-CL-CURRENT: 435/6; 435/91.1, 435/91.2, 536/23.1, 536/24.3, 536/24.31, 536/24.33

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 7. Document ID: US 5776348 A

L1: Entry 7 of 11 File: USPT Jul 7, 1998

US-PAT-NO: 5776348
DOCUMENT-IDENTIFIER: US 5776348 A

TITLE: Mineral precipitation system and method for inhibiting mineral precipitate formation

DATE-ISSUED: July 7, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Selengut; Jeremy D.	Brookline	MA		
Orme-Johnson; William H.	Cambridge	MA		
Dretler; Stephen P.	Whayland	MA		
Asakura; Hirotaka	Arlington	MA		

US-CL-CURRENT: 210/698; 210/702

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 8. Document ID: US 5702920 A

L1: Entry 8 of 11 File: USPT Dec 30, 1997

US-PAT-NO: 5702920
DOCUMENT-IDENTIFIER: US 5702920 A

TITLE: DNAS encoding human macrophage migration inhibition factor related peptides

DATE-ISSUED: December 30, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Odink; Karel Gerrit	Rheinfelden			CH
Clerc; Roger	Basel			CH
Cerletti; Nico	Bottmingen			CH
Bruggen; Josef	Riehen			CH
Tarcsay; Lajos	Grenzach-Wyhlen			DE
Sorg; Clemens	Munster			DE
Wiesendanger; Walter	Munchenstein			CH

US-CL-CURRENT: 435/69.5; 435/252.33, 435/320.1, 435/325, 435/91.4, 530/351, 530/412, 530/413, 536/23.5, 536/25.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 9. Document ID: US 5350687 A

L1: Entry 9 of 11 File: USPT Sep 27, 1994

US-PAT-NO: 5350687
DOCUMENT-IDENTIFIER: US 5350687 A

TITLE: Antibodies which bind to novel lymphokine related peptides

DATE-ISSUED: September 27, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Odink; Karel G.	Rheinfelden			CH
Clerc; Roger	Basle			CH
Cerletti; Nico	Bottmingen			CH
Bruggen; Josef	Riehen			CH
Tarcsay; Lajos	Grenzach-Wyhlen			DE
Sorg; Clemens	Munster			DE
Wiesendanger; Walter	Munchenstein			CH

US-CL-CURRENT: 435/335; 530/324, 530/387.1, 530/387.9, 530/388.1, 530/388.23, 530/391.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 10. Document ID: EP 263072 A2

L1: Entry 10 of 11 File: EPAB Apr 6, 1988

PUB-NO: EP000263072A2
DOCUMENT-IDENTIFIER: EP 263072 A2
TITLE: Novel lymphokine related peptides.

PUBN-DATE: April 6, 1988

INVENTOR-INFORMATION:

NAME	COUNTRY
ODINK, KAREL GERRIT DR	
CLERC, ROGER DR	
CERLETTI, NICO DR	
BRUGGEN, JOSEF DR	
TARCSAY, LAJOS DR	
SORG, CLEMENS PROF DR	
WIESENDANGER, WALTER	

US-CL-CURRENT: 435/69.5
INT-CL (IPC): A61K 37/02; A61K 39/395; C07K 3/20; C07K 15/00; C12N 5/00; C12P 21/00; C12P 21/02; G01N 33/577; G01N 33/68
EUR-CL (EPC): C07K014/52; C12N015/85, C07K016/24

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 11. Document ID: US 5702920 A EP 263072 A NO 8704159 A ZA 8707417 A FI 8704287 A AU 8779309 A DK 8705177 A JP 63157997 A PT 85849 A NO 9201024 A EP 263072 B1 DE 3789413 G ES 2052602 T3 US 5350687 A JP 09188698 A

L1: Entry 11 of 11 File: DWPI Dec 30, 1997

DERWENT-ACC-NO: 1988-093533
DERWENT-WEEK: 199807

TITLE: Human macrophage migration inhibition factor related peptide - having immune regulating properties for therapeutic use and used for prodn. of antibodies

INVENTOR: BRUEGGEN, J; CERLETTI, N ; CLERC, R ; ODINK, K ; SORG, C ; TARCSAY, L ; WIESENDANGER, W ; BRUGGEN, J ; ODINK, K G ; WIESENDANG, W

PRIORITY-DATA: 1986GB-0028358 (November 27, 1986), 1986GB-0023850 (October 3, 1986)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5702920 A	December 30, 1997		062	C07K014/52
EP 263072 A	April 6, 1988	E	072	
NO 8704159 A	May 2, 1988		000	
ZA 8707417 A	April 5, 1988		000	
FI 8704287 A	April 4, 1988		000	
AU 8779309 A	May 19, 1988		000	
DK 8705177 A	April 4, 1988		000	
JP 63157997 A	June 30, 1988		000	
PT 85849 A	November 30, 1988		000	
NO 9201024 A	April 5, 1988		000	C12N015/00
EP 263072 B1	March 23, 1994	E	117	C12P021/02
DE 3789413 G	April 28, 1994		000	C12P021/02
ES 2052602 T3	July 16, 1994		000	C12P021/02
US 5350687 A	September 27, 1994		051	C07K005/00
JP 09188698 A	July 22, 1997		065	C07K014/52

INT-CL (IPC): A61K 37/02; A61K 38/00; A61K 39/39; A61K 39/395; C07G 17/00; C07H 21/04; C07K 3/20; C07K 5/00; C07K 7/10; C07K 13/00; C07K 14/52; C07K 15/00; C07K 15/28; C07K 16/24; C12N 1/16; C12N 1/19; C12N 1/20; C12N 1/21; C12N 5/00; C12N 5/10; C12N 5/12; C12N 15/00; C12N 15/09; C12N 15/19; C12N 21/00; C12P 19/34; C12P 21/00; C12P 21/02; C12P 21/08; G01N 33/50; G01N 33/53; G01N 33/54; G01N 33/577; G01N 33/68; C12P 21/00; C12R 1/91 ; C12P 21/02; C12R 1/19; C12P 21/02; C12R 1/91; C12P 21/02; C12R 1/865

Term	Documents
MSRP-8	0
MSRP-8S	0
MRP-14.DWPI,TDBD,EPAB,USPT,PGPB.	11
MRP-14S	0
(MSRP-8 OR MRP-14).USPT,PGPB,EPAB,DWPI,TDBD.	11
(MSRP-8 OR MRP-14).USPT,PGPB,EPAB,DWPI,TDBD.	11

WEST Search History

DATE: Wednesday, April 16, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,EPAB,DWPI,TDBD; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L9	l7 and (intimal same injury)	0	L9
L8	L5 and secretion	17	L8
L7	L5 and (granule adj secretion)	0	L7
L6	L5 and (granule adj secret$)	0	L6
L5	(calgranulin or mrp-8 or mrp-14)	82	L5
L4	(calgranulin or mrp-8 or mrp-14) and(granule adj secret$)	0	L4
L3	(calgranulin or mrp-8 or mrp-14) same (granule adj secret$)	0	L3
L2	fukuda-kouichirou.in.	1	L2
L1	seto-minoru.in.	5	L1

END OF SEARCH HISTORY

WEST

Generate Collection | Print

Search Results - Record(s) 1 through 82 of 82 returned.

☐ 1. Document ID: US 20030065156 A1

L5: Entry 1 of 82 File: PGPB Apr 3, 2003

PGPUB-DOCUMENT-NUMBER: 20030065156
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030065156 A1

TITLE: Novel human genes and gene expression products I

PUBLICATION-DATE: April 3, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Williams, Lewis T.	Mill Valley	CA	US	
Escobedo, Jaime	Alamo	CA	US	
Innis, Michael A.	Moraga	CA	US	
Garcia, Pablo Dominguez	San Francisco	CA	US	
Sudduth-Klinger, Julie	Kensington	CA	US	
Reinhard, Christoph	Alameda	CA	US	
Giese, Klause	San Francisco	CA	US	
Randazzo, Filippo	Emeryville	CA	US	
Kennedy, Giulia C.	San Francisco	CA	US	
Pot, David	San Francisco	CA	US	
Kassam, Atlaf	Oakland	CA	US	
Lamson, George	Moraga	CA	US	
Drmanac, Radoje	Palo Alto	CA	US	
Crkvenjakov, Radomir	Sunnyvale	CA	US	
Dickson, Mark	Hollister	CA	US	
Drmanac, Snezana	Palo Alto	CA	US	
Labat, Ivan	Sunnyvale	CA	US	
Leshkowitz, Dena	Sunnyvale	CA	US	
Kita, David	Foster City	CA	US	
Garcia, Veronica	Sunnyvale	CA	US	
Jones, Lee William	Sunnyvale	CA	US	
Stache-Crain, Birgit	Sunnyvale	CA	US	

US-CL-CURRENT: 536/23.1; 435/6, 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20030054387 A1

L5: Entry 2 of 82 File: PGPB Mar 20, 2003

PGPUB-DOCUMENT-NUMBER: 20030054387
PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030054387 A1

TITLE: Metastasis-associated genes

PUBLICATION-DATE: March 20, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Chen, Jeremy J.W.	Fengyuan City		TW	
Yang, Pan-Chyr	Taipei		TW	
Peck, Konan	Taipei		TW	
Hong, Tse-Ming	Taipei		TW	
Yang, Shuenn-Chen	Taipei		TW	
Wu, Cheng-Wen	Taipei		TW	

US-CL-CURRENT: 435/6; 702/20

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 3. Document ID: US 20030036070 A1

L5: Entry 3 of 82 File: PGPB Feb 20, 2003

PGPUB-DOCUMENT-NUMBER: 20030036070
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030036070 A1

TITLE: Gene expression profiling of inflammatory bowel disease

PUBLICATION-DATE: February 20, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Chakravarti, Shukti	Lutherville	MD	US	

US-CL-CURRENT: 435/6; 435/91.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 20030032663 A1

L5: Entry 4 of 82 File: PGPB Feb 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030032663
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030032663 A1

TITLE: Benzimidazole derivatives as therapeutic agents

PUBLICATION-DATE: February 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
M. Mjalli, Adnan M.	Jamestown	NC	US	
Gopalaswamy, Ramesh	Jamestown	NC	US	

US-CL-CURRENT: 514/394; 548/304.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 20030022242 A1

L5: Entry 5 of 82 File: PGPB Jan 30, 2003

PGPUB-DOCUMENT-NUMBER: 20030022242
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030022242 A1

TITLE: Particles with improved solubilization capacity

PUBLICATION-DATE: January 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Anderson, David	Colonial Heights	VA	US	

US-CL-CURRENT: 435/7.1; 424/490

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 20030003482 A1

L5: Entry 6 of 82 File: PGPB Jan 2, 2003

PGPUB-DOCUMENT-NUMBER: 20030003482
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030003482 A1

TITLE: MRP8/MRP14 heterodimer, or its individual components in combination, for treating and/or preventing skin diseases, wounds and/or wound-healing disturbances, having a reduced quantity of MRP8/MRP14 heterodimers

PUBLICATION-DATE: January 2, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Halle, Jorn-Peter	Penzberg		DE	
Goppelt, Andreas	Munchen		DE	

US-CL-CURRENT: 435/6; 435/7.21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 7. Document ID: US 20020197633 A1

L5: Entry 7 of 82 File: PGPB Dec 26, 2002

PGPUB-DOCUMENT-NUMBER: 20020197633
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020197633 A1

TITLE: Evaluation of ultraviolet radiation damage to skin using new gene markers, methods and compositions related thereto

PUBLICATION-DATE: December 26, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Jones, Brian C.	Warwick	NY	US	
Bosko, Carol	Oradell	NY	US	
Cooper, Kevin	Moreland Hills	OH	US	
McCormick, Thomas	Orange Village	OH	US	

US-CL-CURRENT: 435/6; 435/448, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 8. Document ID: US 20020193432 A1

L5: Entry 8 of 82 File: PGPB Dec 19, 2002

PGPUB-DOCUMENT-NUMBER: 20020193432
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020193432 A1

TITLE: Carboxamide derivatives as therapeutic agents

PUBLICATION-DATE: December 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Mjalli, Adnan M. M.	Jamestown	NC	US	
Andrews, Robert C.	Jamestown	NC	US	
Gopalaswamy, Ramesh	Jamestown	NC	US	
Wysong, Chris	Winston-Salem	NC	US	

US-CL-CURRENT: 514/478; 514/617, 514/626, 560/159, 564/161

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 9. Document ID: US 20020192228 A1

L5: Entry 9 of 82 File: PGPB Dec 19, 2002

PGPUB-DOCUMENT-NUMBER: 20020192228
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020192228 A1

TITLE: PROTEIN MARKERS FOR LUNG CANCER AND USE THEREOF

PUBLICATION-DATE: December 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
HANASH, SAMIR M.	ANN ARBOR	MI	US	

US-CL-CURRENT: 424/185.1; 424/130.1, 514/2, 530/300, 530/350, 530/387.1, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 10. Document ID: US 20020173622 A1

L5: Entry 10 of 82 File: PGPB Nov 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020173622
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020173622 A1

TITLE: Tsg101-GAGp6 interaction and use thereof

PUBLICATION-DATE: November 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wettstein, Daniel Albert	Salt Lake City	UT	US	
Morham, Scott	Salt Lake City	UT	US	
Zavitz, Kenton	Salt Lake City	UT	US	

US-CL-CURRENT: 530/350; 435/320.1, 530/826

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 11. Document ID: US 20020156054 A1

L5: Entry 11 of 82 File: PGPB Oct 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020156054
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020156054 A1

TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

PUBLICATION-DATE: October 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Klein, Elliott S.	Marina del Rey	CA	US	
Johnson, Alan T.	Rancho Santa Margarita	CA	US	
Standeven, Andrew M.	Corona del Mar	CA	US	
Beard, Richard L.	Newport Beach	CA	US	
Gillett, Samuel J.	Albany	CA	US	
Duong, Tien T.	Irvine	CA	US	
Nagpal, Sunil	Irvine	CA	US	
Vuligonda, Vidyasagar	Irvine	CA	US	
Teng, Min	Aliso Viejo	CA	US	
Chandraratna, Roshantha A.	Mission Viejo	CA	US	

US-CL-CURRENT: 514/150; 514/311, 514/434, 514/456, 514/529, 514/599, 514/617, 534/751, 534/787, 546/171, 546/177, 549/23 , 549/398

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 12. Document ID: US 20020122799 A1

L5: Entry 12 of 82 File: PGPB Sep 5, 2002

PGPUB-DOCUMENT-NUMBER: 20020122799
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020122799 A1

TITLE: Methods for treating inflammation

PUBLICATION-DATE: September 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Stern, David M.	Great Neck	NY	US	
Herold, Kevan	Scarsdale	NY	US	
Yan, Shi Du	Tenafly	NJ	US	
Schmidt, Ann Marie	Franklin Lakes	NJ	US	
Lamster, Ira	Wycoff	NJ	US	

US-CL-CURRENT: 424/143.1; 514/12, 514/23, 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 13. Document ID: US 20020116725 A1

L5: Entry 13 of 82 File: PGPB Aug 22, 2002

PGPUB-DOCUMENT-NUMBER: 20020116725
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020116725 A1

TITLE: Method to increase cerebral blood flow in amyloid angiopathy

PUBLICATION-DATE: August 22, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Stern, David M.	Great Neck	NY	US	
Schmidt, Ann Marie	Franklin Lakes	NJ	US	
Yan, Shi Du	New York	NY	US	
Zlokovic, Berislav	Rochester	NY	US	

US-CL-CURRENT: 800/12; 514/12, 514/44, 800/18

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 14. Document ID: US 20020106726 A1

L5: Entry 14 of 82 File: PGPB Aug 8, 2002

PGPUB-DOCUMENT-NUMBER: 20020106726
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020106726 A1

TITLE: Extracellular novel RAGE binding protein (EN-RAGE) and uses thereof

PUBLICATION-DATE: August 8, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Schmidt, Ann Marie	Franklin Lakes	NJ	US	
Stern, David	Great Neck	NY	US	

US-CL-CURRENT: 435/69.1; 435/320.1, 435/325, 530/350, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 15. Document ID: US 20020102589 A1

L5: Entry 15 of 82 File: PGPB Aug 1, 2002

PGPUB-DOCUMENT-NUMBER: 20020102589
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020102589 A1

TITLE: Microarrays and methods for evaluating activity of compounds having estrogen-like activity

PUBLICATION-DATE: August 1, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Kiyama, Ryoiti	Ibaraki		JP	
Oguchi, Shinobu	Tokyo		JP	

US-CL-CURRENT: 435/6; 702/20

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 16. Document ID: US 20020090625 A1

L5: Entry 16 of 82 File: PGPB Jul 11, 2002

PGPUB-DOCUMENT-NUMBER: 20020090625
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020090625 A1

TITLE: Methods of detecting cancer based on prostasin

PUBLICATION-DATE: July 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Mok, Samuel C.	Brookline	MA	US	
Wong, Kwong-Kwok	Sugar Land	TX	US	

US-CL-CURRENT: 435/6; 435/7.23, 435/7.92

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 17. Document ID: US 20020086282 A1

L5: Entry 17 of 82 File: PGPB Jul 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020086282
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020086282 A1

TITLE: Methods and compositions for detecting compounds that modulate inflammatory responses

PUBLICATION-DATE: July 4, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Pillarisetti, Sivaram	Norcross	GA	US	
Cahoon, Shianlen	Atlanta	GA	US	
Saxena, Uday	Atlanta	GA	US	

US-CL-CURRENT: 435/4; 435/6, 435/7.21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 18. Document ID: US 20020042366 A1

L5: Entry 18 of 82 File: PGPB Apr 11, 2002

PGPUB-DOCUMENT-NUMBER: 20020042366
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020042366 A1

TITLE: Method for treating inflammation

PUBLICATION-DATE: April 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Thompson, Penny	Snohomish	WA	US	
Foster, Donald C.	Lake Forest Park	WA	US	
Xu, Wenfeng	Mukilteo	WA	US	
Madden, Karen L.	Bellevue	WA	US	
Kelly, James D.	Mercer Island	WA	US	
Sprecher, Cindy A.	Seattle	WA	US	
Blumberg, Hal	Seattle	WA	US	
Eagan, Maribeth A.	Seattle	WA	US	
Jaspers, Stephen R.	Edmonds	WA	US	
Chandrasekher, Yasmin A.	Mercer Island	WA	US	
Novak, Julia E.	Bainbridge Island	WA	US	

US-CL-CURRENT: 514/12; 424/145.1, 424/85.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 19. Document ID: US 20020037538 A1

L5: Entry 19 of 82 File: PGPB Mar 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020037538
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020037538 A1

TITLE: Compositions, kits, and methods for identification, assessment, prevention, and therapy of psoriasis

PUBLICATION-DATE: March 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Trepicchio, William L.	Andover	MA	US	
Oestreicher, Judith L.	Portsmouth	NH	US	
Dorner, Andrew J.	Lexington	MA	US	
Krueger, James G.	New York	NY	US	

US-CL-CURRENT: 435/7.21; 435/6

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 20. Document ID: US 20020034773 A1

L5: Entry 20 of 82 File: PGPB Mar 21, 2002

PGPUB-DOCUMENT-NUMBER: 20020034773
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020034773 A1

TITLE: S100 proteins and autoantibodies as serum markers for cancer

PUBLICATION-DATE: March 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hanash, Samir M.	Ann Arbor	MI	US	
Misek, David	Ann Arbor	MI	US	
Prasannan, Latha	Marshfield	WI	US	

US-CL-CURRENT: 435/7.23

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 21. Document ID: US 20020009730 A1

L5: Entry 21 of 82 File: PGPB Jan 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020009730
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020009730 A1

TITLE: Human stress array

PUBLICATION-DATE: January 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Chenchik, Alex	Palo Alto	CA	US	
Lukashev, Matvey E.	Newton	MA	US	

US-CL-CURRENT: 435/6; 536/24.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 22. Document ID: US 20020006957 A1

L5: Entry 22 of 82 File: PGPB Jan 17, 2002

PGPUB-DOCUMENT-NUMBER: 20020006957
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020006957 A1

TITLE: Method for the synthesis of compounds of formula I and their uses thereof

PUBLICATION-DATE: January 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Mjalli, Adnan M.M.	Jamestown	NC	US	
Gopalaswamy, Ramesh	Greensboro	NC	US	
Avor, Kwasi S.	High Point	NC	US	
Wysong, Christopher L.	Winston-Salem	NC	US	
Patron, Andrew	San Diego	CA	US	

US-CL-CURRENT: 514/510; 514/514, 568/24, 568/48

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 23. Document ID: US 20010036631 A1

L5: Entry 23 of 82 File: PGPB Nov 1, 2001

PGPUB-DOCUMENT-NUMBER: 20010036631
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010036631 A1

TITLE: Evaluating and predicting clinical outcomes by gene expression analysis

PUBLICATION-DATE: November 1, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
McGrath, Michael	Burlingame	CA	US	
Meuer, Stefan	Heldelberg		DE	
Kuehne, Friedrich-Wilhelm	Bangkok		TH	

US-CL-CURRENT: 435/6; 435/5, 435/91.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 24. Document ID: US 6538149 B1

L5: Entry 24 of 82 File: USPT Mar 25, 2003

US-PAT-NO: 6538149
DOCUMENT-IDENTIFIER: US 6538149 B1

TITLE: ARYL OR HETEROARYL SUBSTITUTED 3,4-DIHYDROANTHRACENE AND ARYL OR HETEROARYL SUBSTITUTED BENZO [1,2-G]CHROM-3-ENE, BENZO[1,2-G]-THIOCHROM-3-ENE AND BENZO [1,2-G]-1,2-DIHYDROQUINOLINE DERIVATIVES HAVING RETINOID ANTAGONIST OR RETINOID INVERSE AGONIST TYPE BIOLOGICAL ACTIVITY

DATE-ISSUED: March 25, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vuligonda; Vidyasagar	Irvine	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 560/5; 556/465, 562/400, 562/403, 564/180

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 25. Document ID: US 6521624 B1

L5: Entry 25 of 82 File: USPT Feb 18, 2003

US-PAT-NO: 6521624
DOCUMENT-IDENTIFIER: US 6521624 B1

TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

DATE-ISSUED: February 18, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliott S.	Marina del Ray	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Standeven; Andrew M.	Corona del Mar	CA		
Beard; Richard L.	Newport Beach	CA		
Gillett; Samuel J.	Albany	CA		
Duong; Tien T.	Irvine	CA		
Nagpal; Sunil	Lake Forest	CA		
Vuligonda; Vidyasagar	Irvine	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 514/252.12; 514/311, 514/432, 514/453

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 26. Document ID: US 6518013 B1

L5: Entry 26 of 82 File: USPT Feb 11, 2003

US-PAT-NO: 6518013
DOCUMENT-IDENTIFIER: US 6518013 B1

TITLE: Methods for the inhibition of epstein-barr virus transmission employing anti-viral peptides capable of abrogating viral fusion and transmission

DATE-ISSUED: February 11, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 435/5; 424/230.1, 530/300, 530/324, 530/325, 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 27. Document ID: US 6509033 B1

L5: Entry 27 of 82 File: USPT Jan 21, 2003

US-PAT-NO: 6509033
DOCUMENT-IDENTIFIER: US 6509033 B1

TITLE: Immunomodulatory peptides

DATE-ISSUED: January 21, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Urban; Robert Glen	Cambridge	MA		
Chicz; Roman M.	Jamaica Plain	MA		
Vignali; Dario A. A.	Rainham			GB
Hedley; Mary Lynne	Somerville	MA		
Stern; Lawrence J.	Arlington	MA		
Strominger; Jack L.	Lexington	MA		

US-CL-CURRENT: 424/450; 435/320.1, 514/44, 536/23.1, 536/23.2, 536/23.4, 536/23.5, 536/23.51, 536/23.52, 536/23.53, 536/23.7, 536/23.72

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 28. Document ID: US 6479055 B1

L5: Entry 28 of 82 File: USPT Nov 12, 2002

US-PAT-NO: 6479055
DOCUMENT-IDENTIFIER: US 6479055 B1

TITLE: Methods for inhibition of membrane fusion-associated events, including respiratory syncytial virus transmission

DATE-ISSUED: November 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bolognesi; Dani Paul	Durham	NC		
Matthews; Thomas James	Durham	NC		
Wild; Carl T.	Durham	NC		
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		
Langlois; Alphonse J.	Durham	NC		

US-CL-CURRENT: 424/211.1; 424/186.1, 530/324

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 29. Document ID: US 6469028 B1

L5: Entry 29 of 82 File: USPT Oct 22, 2002

US-PAT-NO: 6469028
DOCUMENT-IDENTIFIER: US 6469028 B1

TITLE: Synthesis and use of retinoid compounds having negative hormone and/or anatgonist activities

DATE-ISSUED: October 22, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliott S.	Marina del Rey	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Standeven; Andrew M.	Corona del Mar	CA		
Beard; Richard L.	Newport Beach	CA		
Gillett; Samuel J.	Albany	CA		
Duong; Tien T.	Irvine	CA		
Nagpal; Sunil	Lake Forest	CA		
Vuligonda; Vidyasagar	Irvine	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 514/311; 514/314, 514/432, 514/456, 546/167, 546/168, 549/23, 549/362

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 30. Document ID: US 6465647 B1

L5: Entry 30 of 82 File: USPT Oct 15, 2002

US-PAT-NO: 6465647
DOCUMENT-IDENTIFIER: US 6465647 B1

TITLE: Oxygen, sulfur and nitrogen substituted cyclohexene and cyclohexane derivatives having retinoid-like biological activity

DATE-ISSUED: October 15, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Beard; Richard L.	Newport Beach	CA		
Colon; Diana F.	Newport Beach	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 544/224; 544/242, 544/336, 546/340, 546/348, 548/204, 548/235, 548/341.5, 548/373.1, 549/229, 549/78, 549/80, 558/234, 558/248, 558/250, 558/257, 558/260, 558/275, 564/161, 564/182, 564/74

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 31. Document ID: US 6465646 B1

L5: Entry 31 of 82 File: USPT Oct 15, 2002

US-PAT-NO: 6465646
DOCUMENT-IDENTIFIER: US 6465646 B1

TITLE: 1-alkoxy and 1-acyloxy substituted cyclohex-1-ene compounds and sulfur and 1-alkoxycarbonyl analogs having retinoid-like biological activity

DATE-ISSUED: October 15, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Beard; Richard L.	Newport Beach	CA		
Colon; Diana F.	Newport Beach	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 544/224; 544/242, 544/336, 546/340, 546/348, 548/204, 548/235, 548/341.5, 548/373.1, 549/229, 549/78, 549/80

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 32. Document ID: US 6455701 B1

L5: Entry 32 of 82 File: USPT Sep 24, 2002

US-PAT-NO: 6455701
DOCUMENT-IDENTIFIER: US 6455701 B1

TITLE: Substituted diaryl or diheteroaryl methanes, ethers and amines having retinoid agonist, antagonist or inverse agonist type biological activity

DATE-ISSUED: September 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Song; Tae K.	Long Beach	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 546/322; 546/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 33. Document ID: US 6403638 B1

L5: Entry 33 of 82 File: USPT Jun 11, 2002

US-PAT-NO: 6403638
DOCUMENT-IDENTIFIER: US 6403638 B1

TITLE: 2,4-pentadienoic acid derivatives having selective activity for retinoid X (RXR) receptors

DATE-ISSUED: June 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vuligonda; Vidyasagar	Irvine	CA		
Tsang; Kwok Yin	Irvine	CA		
Vasudevan; Jayasree	Irvine	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 514/457; 514/510, 514/531, 514/557, 514/569, 514/570, 549/362, 549/407, 549/408, 549/548, 549/549, 549/551, 560/102, 560/124, 560/20, 560/21, 560/23, 562/433, 562/434, 562/462, 562/466, 562/469, 562/492

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 34. Document ID: US 6235923 B1

L5: Entry 34 of 82 File: USPT May 22, 2001

US-PAT-NO: 6235923
DOCUMENT-IDENTIFIER: US 6235923 B1
**** See image for Certificate of Correction ****

TITLE: Trisubstituted phenyl derivatives having retinoid agonist, antagonist or inverse agonist type biological activity

DATE-ISSUED: May 22, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Song; Tae K.	Long Beach	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 560/52; 560/101, 560/57, 562/460, 562/463, 562/491

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 35. Document ID: US 6228983 B1

L5: Entry 35 of 82 File: USPT May 8, 2001

US-PAT-NO: 6228983
DOCUMENT-IDENTIFIER: US 6228983 B1
**** See image for Certificate of Correction ****

TITLE: Human respiratory syncytial virus peptides with antifusogenic and antiviral activities

DATE-ISSUED: May 8, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 530/300; 424/186.1, 424/211.1, 530/324, 530/325, 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 36. Document ID: US 6228848 B1

L5: Entry 36 of 82 File: USPT May 8, 2001

US-PAT-NO: 6228848
DOCUMENT-IDENTIFIER: US 6228848 B1

TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

DATE-ISSUED: May 8, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliott S.	Marina del Rey	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Standeven; Andrew M.	Corona del Mar	CA		
Beard; Richard L.	Newport Beach	CA		
Gillett; Samuel J.	Albany	CA		
Duong; Tien T.	Irvine	CA		
Nagpal; Sunil	Lake Forest	CA		
Vuligonda; Vidyasagar	Irvine	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 514/63; 514/247, 514/252.01, 514/255.05, 514/256, 514/342, 514/365, 514/374, 514/397, 514/399, 514/406, 544/224, 544/238, 544/242, 544/333, 544/336, 544/405, 546/268.4, 546/340, 548/187, 548/236, 548/315.1, 548/324.1, 548/364.1, 548/376.1, 549/473, 549/498, 549/59, 549/78, 549/79, 560/51

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 37. Document ID: US 6225494 B1

L5: Entry 37 of 82 File: USPT May 1, 2001

US-PAT-NO: 6225494
DOCUMENT-IDENTIFIER: US 6225494 B1
**** See image for Certificate of Correction ****

TITLE: Trisubstituted phenyl derivatives having retinoid agonist or inverse agonist type biological activity

DATE-ISSUED: May 1, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Song; Tae K.	Long Beach	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 560/52; 560/101, 560/57, 562/401, 562/460, 562/463

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 38. Document ID: US 6218128 B1

L5: Entry 38 of 82 File: USPT Apr 17, 2001

US-PAT-NO: 6218128
DOCUMENT-IDENTIFIER: US 6218128 B1

TITLE: Methods of identifying compounds having nuclear receptor negative hormone and/or antagonist activities

DATE-ISSUED: April 17, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliott S.	Marina Del Rey	CA		
Nagpal; Sunil	Lake Forest	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 39. Document ID: US 6187950 B1

L5: Entry 39 of 82 File: USPT Feb 13, 2001

US-PAT-NO: 6187950
DOCUMENT-IDENTIFIER: US 6187950 B1

TITLE: Substituted diaryl or diheteroaryl methanes, ethers and amines having retinoid agonist, antagonist or inverse agonist type biological

DATE-ISSUED: February 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Song; Tae K.	Long Beach	CA	90807	
Teng; Min	Aliso Viejo	CA	92656	
Chandraratna; Roshantha A.	Mission Viejo	CA	92691	

US-CL-CURRENT: 562/474; 560/65, 560/67, 562/473, 562/475

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 40. Document ID: US 6177588 B1

L5: Entry 40 of 82 File: USPT Jan 23, 2001

US-PAT-NO: 6177588
DOCUMENT-IDENTIFIER: US 6177588 B1

TITLE: 1-alkoxy and 1-acyloxy substituted cyclohex-1-ene compounds and sulfur and 1-alkoxycarbonyl analogs having retinoid-like biological activity

DATE-ISSUED: January 23, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Beard; Richard L.	Newport Beach	CA		
Colon; Diana F.	Newport Beach	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 560/76; 556/437, 556/440, 558/52, 560/81

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 41. Document ID: US 6166244 A

L5: Entry 41 of 82 File: USPT Dec 26, 2000

US-PAT-NO: 6166244
DOCUMENT-IDENTIFIER: US 6166244 A
**** See image for Certificate of Correction ****

TITLE: Oxygen, sulfur and nitrogen substituted cyclohexene and cyclohexane derivatives having retinoid-like biological activity

DATE-ISSUED: December 26, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Beard; Richard L.	Newport Beach	CA		
Colon; Diana F.	Newport Beach	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 560/64; 556/440, 560/107, 560/194, 560/81, 560/85

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 42. Document ID: US 6147224 A

L5: Entry 42 of 82 File: USPT Nov 14, 2000

US-PAT-NO: 6147224
DOCUMENT-IDENTIFIER: US 6147224 A
**** See image for Certificate of Correction ****

TITLE: 2,4-pentadienoic acid derivatives having selective activity for retinoid X (RXR) receptors

DATE-ISSUED: November 14, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vuligonda; Vidyasagar	Irvine	CA		
Tsang; Kwok Yin	Irvine	CA		
Vasudevan; Jayasree	Irvine	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 548/518; 548/566, 548/567, 548/570, 548/571, 548/572, 549/391, 549/407, 549/408, 549/409, 549/548, 549/549, 549/551, 549/553, 549/554, 549/556, 549/557, 549/559, 549/563, 560/102, 560/14, 560/20, 560/21, 560/23, 560/24, 562/433, 562/434, 562/462, 562/466, 562/469, 562/492, 564/164, 564/165, 564/166, 564/167 , 568/307, 568/325, 568/327, 568/440, 568/441, 568/442, 568/592, 568/661, 568/705, 568/715, 568/808

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 43. Document ID: US 6127382 A

L5: Entry 43 of 82 File: USPT Oct 3, 2000

US-PAT-NO: 6127382
DOCUMENT-IDENTIFIER: US 6127382 A

TITLE: Amines substituted with a tetrahydroquinolinyl group an aryl or heteroaryl group and an alkyl group, having retinoid-like biological activity

DATE-ISSUED: October 3, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Beard; Richard L.	Newport Beach	CA		
Jeon; Raok	Irvine	CA		
Colon; Diana F.	Newport Beach	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 514/311; 514/252.02, 514/252.04, 514/252.11, 514/255.05, 514/312, 514/314, 544/238, 544/405, 546/158, 546/165

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 44. Document ID: US 6093838 A

L5: Entry 44 of 82 File: USPT Jul 25, 2000

US-PAT-NO: 6093838
DOCUMENT-IDENTIFIER: US 6093838 A

TITLE: Amines substituted with a dihydro-benzofuranyl or with a dihydro-isobenzofuranyl group, an aryl or heteroaryl group and an alkyl group, having retinoid-like biological activity

DATE-ISSUED: July 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vasudevan; Jayasree	Irvine	CA		
Beard; Richard L.	Newport Beach	CA		
Huang; Dehua	San Diego	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 549/467; 544/322, 546/284.1, 548/190, 548/311.4, 549/60

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 45. Document ID: US 6093794 A

L5: Entry 45 of 82 File: USPT Jul 25, 2000

US-PAT-NO: 6093794
DOCUMENT-IDENTIFIER: US 6093794 A

TITLE: Isolated peptides derived from the Epstein-Barr virus containing fusion inhibitory domains

DATE-ISSUED: July 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 530/300; 424/186.1, 424/230.1, 530/324, 530/325, 530/326, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 46. Document ID: US 6090810 A

L5: Entry 46 of 82 File: USPT Jul 18, 2000

US-PAT-NO: 6090810
DOCUMENT-IDENTIFIER: US 6090810 A

TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

DATE-ISSUED: July 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliott S.	Marina del Rey	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Standeven; Andrew M.	Corona del Mar	CA		
Beard; Richard L.	Newport Beach	CA		
Gillett; Samuel J.	Albany	CA		
Duong; Tien T.	Irvine	CA		
Nagpal; Sunil	Lake Forest	CA		
Vuligonda; Vidyasagar	Irvine	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 514/252.01; 514/150, 514/252.05, 514/255.05, 534/767, 534/768, 549/404, 549/405, 549/406, 549/410

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 47. Document ID: US 6087505 A

L5: Entry 47 of 82 File: USPT Jul 11, 2000

US-PAT-NO: 6087505
DOCUMENT-IDENTIFIER: US 6087505 A

TITLE: Benzo[1,2-G]-chrom-3-ene, and benzo[1,2-G]-thiochrom-3-ene derivatives

DATE-ISSUED: July 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vuligonda; Vidyasagar	Irvine	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 546/281.1; 546/268.1, 546/279.7, 546/281.7, 546/284.7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 48. Document ID: US 6087123 A

L5: Entry 48 of 82 File: USPT Jul 11, 2000

US-PAT-NO: 6087123
DOCUMENT-IDENTIFIER: US 6087123 A.

TITLE: Metal-containing ribonucleotide polypeptides

DATE-ISSUED: July 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wissler; Josef	Bad Nauheim			DE
Logemann; Enno	Freiburg			DE
Kiesewetter; Stefan	Lautertal-Unterlauter			DE
Heilmeyer; Ludwig	Bochum			DE

US-CL-CURRENT: 435/69.1; 435/6, 435/91.1, 435/91.3, 530/300, 530/324, 530/412, 536/23.1, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 49. Document ID: US 6068973 A

L5: Entry 49 of 82 File: USPT May 30, 2000

US-PAT-NO: 6068973
DOCUMENT-IDENTIFIER: US 6068973 A

TITLE: Methods for inhibition of membrane fusion-associated events, including influenza virus

DATE-ISSUED: May 30, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 435/5; 424/147.1, 424/206.1, 424/230.1, 530/324, 530/389.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 50. Document ID: US 6060065 A

L5: Entry 50 of 82 File: USPT May 9, 2000

US-PAT-NO: 6060065
DOCUMENT-IDENTIFIER: US 6060065 A

TITLE: Compositions for inhibition of membrane fusion-associated events, including influenza virus transmission

DATE-ISSUED: May 9, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 424/209.1; 424/186.1, 424/192.1, 424/206.1, 530/300, 530/324, 530/325, 530/326, 530/327, 530/328, 530/329 , 530/330

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 51. Document ID: US 6054265 A

L5: Entry 51 of 82 File: USPT Apr 25, 2000

US-PAT-NO: 6054265
DOCUMENT-IDENTIFIER: US 6054265 A

TITLE: Screening assays for compounds that inhibit membrane fusion-associated events

DATE-ISSUED: April 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway, Jr.; Stephen Robert	Cary	NC		

US-CL-CURRENT: 435/5; 435/7.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 52. Document ID: US 6048873 A

L5: Entry 52 of 82 File: USPT Apr 11, 2000

US-PAT-NO: 6048873
DOCUMENT-IDENTIFIER: US 6048873 A
**** See image for Certificate of Correction ****

TITLE: Tetrahdroquinolin-2-one 6 or 7-yl, tetrahdroquinilin-2-thione 6 or 7-yl pentadienoic acid and related derivatives having retinoid-like biological activity

DATE-ISSUED: April 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vasudevan; Jayasree	Irvine	CA		
Vuligonda; Vidyasagar	Irvine	CA		
Beard; Richard L.	Newport Beach	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 514/311; 546/165

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 53. Document ID: US 6037488 A

L5: Entry 53 of 82 File: USPT Mar 14, 2000

US-PAT-NO: 6037488
DOCUMENT-IDENTIFIER: US 6037488 A

TITLE: Trisubstituted phenyl derivatives having retinoid agonist, antagonist or inverse agonist type biological activity

DATE-ISSUED: March 14, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Song; Tae K.	Long Beach	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 560/52; 560/101, 560/57, 562/460, 562/463, 562/491

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 54. Document ID: US 6017536 A

L5: Entry 54 of 82 File: USPT Jan 25, 2000

US-PAT-NO: 6017536
DOCUMENT-IDENTIFIER: US 6017536 A

TITLE: Simian immunodeficiency virus peptides with antifusogenic and antiviral activities

DATE-ISSUED: January 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		
Langlois; Alphonse J.	Durham	NC		

US-CL-CURRENT: 424/188.1; 424/208.1, 530/300, 530/324, 530/325, 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 55. Document ID: US 6013263 A

L5: Entry 55 of 82 File: USPT Jan 11, 2000

US-PAT-NO: 6013263
DOCUMENT-IDENTIFIER: US 6013263 A

TITLE: Measles virus peptides with antifusogenic and antiviral activities

DATE-ISSUED: January 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Barney; Shawn O'Lin	Cary	NC		
Lambert; Dennis Michael	Cary	NC		
Petteway; Stephen Robert	Cary	NC		

US-CL-CURRENT: 424/212.1; 424/184.1, 424/186.1, 530/300, 530/324, 530/325, 530/326

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 56. Document ID: US 6008204 A

L5: Entry 56 of 82 File: USPT Dec 28, 1999

US-PAT-NO: 6008204
DOCUMENT-IDENTIFIER: US 6008204 A
**** See image for Certificate of Correction ****

TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

DATE-ISSUED: December 28, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliott S.	Marina del Rey	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Standeven; Andrew M.	Corona del Mar	CA		
Beard; Richard L.	Newport Beach	CA		
Gillett; Samuel J.	Albany	CA		
Duong; Tien T.	Irvine	CA		
Nagpal; Sunil	Lake Forest	CA		
Vuligonda; Vidyasagar	Irvine	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 514/63; 514/544, 514/568, 514/569, 514/682, 556/437, 560/51, 562/462, 568/468

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 57. Document ID: US 5994076 A

L5: Entry 57 of 82 File: USPT Nov 30, 1999

US-PAT-NO: 5994076
DOCUMENT-IDENTIFIER: US 5994076 A

TITLE: Methods of assaying differential expression

DATE-ISSUED: November 30, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chenchik; Alex	Palo Alto	CA		
Jokhadze; George	Mountain View	CA		
Bibilashvilli; Robert	Moscow			RU

US-CL-CURRENT: 435/6; 435/91.1, 435/91.2, 536/23.1, 536/24.3, 536/24.31, 536/24.33

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 58. Document ID: US 5958954 A

L5: Entry 58 of 82 File: USPT Sep 28, 1999

US-PAT-NO: 5958954
DOCUMENT-IDENTIFIER: US 5958954 A

TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

DATE-ISSUED: September 28, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliott S.	Marina del Rey	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Standeven; Andrew M.	Ventura	CA		
Beard; Richard L.	Newport Beach	CA		
Gillett; Samuel J.	Albany	CA		
Duong; Tien T.	Irvine	CA		
Nagpal; Sunil	Lake Forest	CA		
Vuligonda; Vidyasagar	Irvine	CA		
Teng; Min	San Diego	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 514/333; 514/337, 514/432, 514/456, 546/256, 546/280.1, 546/282.7, 549/396, 549/408, 549/49, 549/51

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 59. Document ID: US 5952345 A

L5: Entry 59 of 82 File: USPT Sep 14, 1999

US-PAT-NO: 5952345
DOCUMENT-IDENTIFIER: US 5952345 A
**** See image for Certificate of Correction ****

TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

DATE-ISSUED: September 14, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliot S.	Marina del Rey	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Standeven; Andrew M.	Corona del Mar	CA		
Beard; Richard L.	Newport Beach	CA		
Gillett; Samuel J.	Albany	CA		
Duong; Tien T.	Irvine	CA		
Nagpal; Sunil	Lake Forest	CA		
Vuligonda; Vidyasagar	Irvine	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 514/311; 514/432, 514/456, 546/169, 546/170, 546/171, 546/173, 549/404, 549/405, 549/406, 549/49, 549/51 , 549/57, 549/58

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 60. Document ID: US 5919970 A

L5: Entry 60 of 82 File: USPT Jul 6, 1999

US-PAT-NO: 5919970
DOCUMENT-IDENTIFIER: US 5919970 A

TITLE: Substituted diaryl or diheteroaryl methanes, ethers and amines having retinoid agonist, antagonist or inverse agonist type biological activity

DATE-ISSUED: July 6, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Song; Tae K.	Long Beach	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 560/48; 560/100, 560/57, 562/405, 562/455, 562/461, 562/467, 562/470, 562/490

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 61. Document ID: US 5880103 A

L5: Entry 61 of 82 File: USPT Mar 9, 1999

US-PAT-NO: 5880103
DOCUMENT-IDENTIFIER: US 5880103 A

TITLE: Immunomodulatory peptides

DATE-ISSUED: March 9, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Urban; Robert Glen	Cambridge	MA		
Chicz; Roman M.	Jamaica Plain	MA		
Vignali; Dario A. A.	Rainham			GB
Hedley; Mary Lynne	Somerville	MA		
Stern; Lawrence J.	Arlington	MA		
Strominger; Jack L.	Lexington	MA		

US-CL-CURRENT: 514/44; 424/93.1, 424/93.2, 424/93.21, 435/235.1, 435/320.1, 435/325, 514/2, 530/300, 536/23.1, 536/23.4 , 536/23.5, 536/23.72

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 62. Document ID: US 5877207 A

L5: Entry 62 of 82 File: USPT Mar 2, 1999

US-PAT-NO: 5877207
DOCUMENT-IDENTIFIER: US 5877207 A
**** See image for Certificate of Correction ****

TITLE: Synthesis and use of retinoid compounds having negative hormone and/or antagonist activities

DATE-ISSUED: March 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliott S.	Marina del Rey	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Standeven; Andrew M.	Corona del Mar	CA		
Beard; Richard L.	Newport Beach	CA		
Gillett; Samuel J.	Oakland	CA		
Duong; Tien T.	Irvine	CA		
Nagpal; Sunil	Irvine	CA		
Vuligonda; Vidyasagar	Irvine	CA		
Teng; Min	Aliso Viejo	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 514/456; 549/405

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 63. Document ID: US 5827516 A

L5: Entry 63 of 82 File: USPT Oct 27, 1998

US-PAT-NO: 5827516
DOCUMENT-IDENTIFIER: US 5827516 A

TITLE: Immunomodulatory peptides

DATE-ISSUED: October 27, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Urban; Robert Glen	Cambridge	MA		
Chicz; Roman M.	Jamaica Plain	MA		
Vignali; Dario A. A.	Rainham			GB
Hedley; Mary Lynne	Somerville	MA		
Stern; Lawrence J.	Arlington	MA		
Strominger; Jack L.	Lexington	MA		

US-CL-CURRENT: 424/93.21; 424/93.2, 424/93.3, 424/93.7, 424/93.71, 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 64. Document ID: US 5776699 A

L5: Entry 64 of 82 File: USPT Jul 7, 1998

US-PAT-NO: 5776699
DOCUMENT-IDENTIFIER: US 5776699 A

TITLE: Method of identifying negative hormone and/or antagonist activities

DATE-ISSUED: July 7, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klein; Elliott S.	Marina Del Rey	CA		
Nagpal; Sunil	Lake Forest	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 435/7.2; 435/320.1, 435/325, 435/69.1, 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 65. Document ID: US 5776348 A

L5: Entry 65 of 82 File: USPT Jul 7, 1998

US-PAT-NO: 5776348
DOCUMENT-IDENTIFIER: US 5776348 A

TITLE: Mineral precipitation system and method for inhibiting mineral precipitate formation

DATE-ISSUED: July 7, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Selengut; Jeremy D.	Brookline	MA		
Orme-Johnson; William H.	Cambridge	MA		
Dretler; Stephen P.	Whayland	MA		
Asakura; Hirotaka	Arlington	MA		

US-CL-CURRENT: 210/698; 210/702

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 66. Document ID: US 5760276 A

L5: Entry 66 of 82 File: USPT Jun 2, 1998

US-PAT-NO: 5760276
DOCUMENT-IDENTIFIER: US 5760276 A
**** See image for Certificate of Correction ****

TITLE: Aryl-and heteroarylcyclohexenyl substituted alkenes having retinoid agonist, antagonist or inverse agonist type biological activity

DATE-ISSUED: June 2, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Beard; Richard L.	Newport Beach	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Teng; Min	Aliso Viejo	CA		
Vuligonda; Vidyasagar	Irvine	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 560/102; 562/492

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 67. Document ID: US 5739338 A

L5: Entry 67 of 82 File: USPT Apr 14, 1998

US-PAT-NO: 5739338
DOCUMENT-IDENTIFIER: US 5739338 A
**** See image for Certificate of Correction ****

TITLE: N-aryl substituted tetrahydroquinolines having retinoid agonist, retinoid antagonist or retinoid inverse agonist type biological activity

DATE-ISSUED: April 14, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Beard; Richard L.	Newport Beach	CA		
Teng; Min	Aliso Viejo	CA		
Colon; Diana F.	Irvine	CA		
Duong; Tien T.	Irvine	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 546/153; 546/165

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 68. Document ID: US 5731166 A

L5: Entry 68 of 82 File: USPT Mar 24, 1998

US-PAT-NO: 5731166
DOCUMENT-IDENTIFIER: US 5731166 A

TITLE: Recombinant production of chemotactic CP-10 polypeptides and therapeutic methods using them

DATE-ISSUED: March 24, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Geczy; Carolyn	Greenwich			AU
Simpson; Richard John	Richmond			AU
Lackmann; Martin	Newport			AU

US-CL-CURRENT: 435/69.1; 435/252.3, 435/254.11, 435/320.1, 435/325, 514/2, 530/350, 530/351, 530/413, 536/23.5, 536/24.31

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 69. Document ID: US 5728846 A

L5: Entry 69 of 82 File: USPT Mar 17, 1998

US-PAT-NO: 5728846
DOCUMENT-IDENTIFIER: US 5728846 A
**** See image for Certificate of Correction ****

TITLE: Benzo[1,2-g]-chrom-3-ene and benzo[1,2-g]-thiochrom-3-ene derivatives

DATE-ISSUED: March 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vuligonda; Vidyasagar	Irvine	CA		
Johnson; Alan T.	Rancho Santa Margarita	CA		
Chandraratna; Roshantha A.	Mission Viejo	CA		

US-CL-CURRENT: 549/16; 544/229, 544/238, 544/333, 544/405, 546/14, 546/281.1, 546/282.7, 546/284.1, 548/146, 548/183, 549/26, 549/389, 549/43, 549/459

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 70. Document ID: US 5702920 A

L5: Entry 70 of 82 File: USPT Dec 30, 1997

US-PAT-NO: 5702920
DOCUMENT-IDENTIFIER: US 5702920 A

TITLE: DNAS encoding human macrophage migration inhibition factor related peptides

DATE-ISSUED: December 30, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Odink; Karel Gerrit	Rheinfelden			CH
Clerc; Roger	Basel			CH
Cerletti; Nico	Bottmingen			CH
Bruggen; Josef	Riehen			CH
Tarcsay; Lajos	Grenzach-Wyhlen			DE
Sorg; Clemens	Munster			DE
Wiesendanger; Walter	Munchenstein			CH

US-CL-CURRENT: 435/69.5; 435/252.33, 435/320.1, 435/325, 435/91.4, 530/351, 530/412, 530/413, 536/23.5, 536/25.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 71. Document ID: US 5350687 A

L5: Entry 71 of 82 File: USPT Sep 27, 1994

US-PAT-NO: 5350687
DOCUMENT-IDENTIFIER: US 5350687 A

TITLE: Antibodies which bind to novel lymphokine related peptides

DATE-ISSUED: September 27, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Odink; Karel G.	Rheinfelden			CH
Clerc; Roger	Basle			CH
Cerletti; Nico	Bottmingen			CH
Bruggen; Josef	Riehen			CH
Tarcsay; Lajos	Grenzach-Wyhlen			DE
Sorg; Clemens	Munster			DE
Wiesendanger; Walter	Munchenstein			CH

US-CL-CURRENT: 435/335; 530/324, 530/387.1, 530/387.9, 530/388.1, 530/388.23, 530/391.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 72. Document ID: WO 2070473 A2

L5: Entry 72 of 82 File: EPAB Sep 12, 2002

PUB-NO: WO002070473A2
DOCUMENT-IDENTIFIER: WO 2070473 A2
TITLE: CARBOXAMIDE DERIVATIVES AS THERAPEUTIC AGENTS

PUBN-DATE: September 12, 2002

INVENTOR-INFORMATION:

NAME	COUNTRY
MJALLI, ADNAN M M	US
ANDREWS, ROB	US
WYSONG, CHRISTOPHER	US

INT-CL (IPC): C07 D 0/
EUR-CL (EPC): C07D211/34; C07C235/38, C07C237/20 , C07C271/22 , C07D207/16 , C07D217/26 , C07D309/04 , C07D521/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 73. Document ID: WO 2069965 A1

L5: Entry 73 of 82 File: EPAB Sep 12, 2002

PUB-NO: WO002069965A1
DOCUMENT-IDENTIFIER: WO 2069965 A1
TITLE: BENZIMIDAZOLE DERIVATIVES AS THERAPEUTIC AGENTS

PUBN-DATE: September 12, 2002

INVENTOR-INFORMATION:

NAME	COUNTRY
MJALLI, ADNAN M M	US
GOPALASWAMY, RAMESH	US

INT-CL (IPC): A61 K 31/4184; C07 D 235/16

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 74. Document ID: EP 263072 A2

L5: Entry 74 of 82 File: EPAB Apr 6, 1988

PUB-NO: EP000263072A2
DOCUMENT-IDENTIFIER: EP 263072 A2
TITLE: Novel lymphokine related peptides.

PUBN-DATE: April 6, 1988

INVENTOR-INFORMATION:

NAME	COUNTRY
ODINK, KAREL GERRIT DR	
CLERC, ROGER DR	
CERLETTI, NICO DR	
BRUGGEN, JOSEF DR	
TARCSAY, LAJOS DR	
SORG, CLEMENS PROF DR	
WIESENDANGER, WALTER	

US-CL-CURRENT: 435/69.5
INT-CL (IPC): A61K 37/02; A61K 39/395; C07K 3/20; C07K 15/00; C12N 5/00; C12P 21/00; C12P 21/02; G01N 33/577; G01N 33/68
EUR-CL (EPC): C07K014/52; C12N015/85, C07K016/24

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 75. Document ID: WO 200269965 A1

L5: Entry 75 of 82 File: DWPI Sep 12, 2002

DERWENT-ACC-NO: 2002-723227
DERWENT-WEEK: 200278
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TITLE: New substituted benzimidazole compounds useful in the treatment of conditions such as atherosclerosis and for the inhibition of the interaction of RAGE

INVENTOR: GOPALASWAMY, R; MJALLI, A M M

PRIORITY-DATA: 2001US-273377P (March 5, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200269965 A1	September 12, 2002	E	060	A61K031/4184

INT-CL (IPC): A61 K 31/4184; C07 D 235/16

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Clip Img | Image

☐ 76. Document ID: US 20020193432 A1 WO 200270473 A2

L5: Entry 76 of 82 File: DWPI Dec 19, 2002

DERWENT-ACC-NO: 2002-698723
DERWENT-WEEK: 200303
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TITLE: New carboxamide derivatives are receptor for advanced glycated end products modulators used for treating e.g. atherosclerosis, Alzheimer's disease and atherosclerosis

INVENTOR: ANDREWS, R C; GOPALASWAMY, R ; MJALLI, A M M ; WYSONG, C ; ANDREWS, R

PRIORITY-DATA: 2001US-273455P (March 5, 2001), 2001US-273403P (March 5, 2001), 2001US-273404P (March 5, 2001), 2001US-273429P (March 5, 2001), 2001US-273445P (March 5, 2001), 2001US-273446P (March 5, 2001), 2001US-273454P (March 5, 2001), 2002US-0091759 (March 5, 2002)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20020193432 A1	December 19, 2002		000	A61K031/325
WO 200270473 A2	September 12, 2002	E	095	C07D000/00

INT-CL (IPC): A61 K 31/165; A61 K 31/325; C07 C 233/07; C07 C 271/08; C07 D 0/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Clip Img | Image

☐ 77. Document ID: WO 200268636 A1 DE 10109466 A1

L5: Entry 77 of 82 File: DWPI Sep 6, 2002

DERWENT-ACC-NO: 2002-706993
DERWENT-WEEK: 200276
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TITLE: New human nucleic acid that forms metallo-ribonucleoprotein complex, useful e.g. for diagnosis and for modulating angiogenesis, e.g. treating tumors

INVENTOR: BRUNNER, H; KOCH-PELSTER, B

PRIORITY-DATA: 2001DE-1009466 (February 28, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200268636 A1	September 6, 2002	G	082	C12N015/11
DE 10109466 A1	September 12, 2002		000	C12N015/12

INT-CL (IPC): A61 K 31/7088; A61 K 38/17; A61 K 48/00; C07 H 21/00; C07 H 21/02; C07 K 14/515; C12 N 1/21; C12 N 15/11; C12 N 15/12; C12 N 15/87

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

☐ 78. Document ID: WO 200192210 A1 AU 200165083 A US 20020006957 A1

L5: Entry 78 of 82 File: DWPI Dec 6, 2001

DERWENT-ACC-NO: 2002-164236
DERWENT-WEEK: 200225
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TITLE: New aminomethylamide compounds are modulators of receptor for advanced glycated end products used for treating e.g. chronic inflammation, diabetes symptoms and Alzheimer's disease

INVENTOR: AVOR, K S; GOPALASWAMY, R ; MJALLI, A M M ; PATRON, A ; WYSONG, C L ; AVOR, K ; MJALLI, A ; WYSONG, C

PRIORITY-DATA: 2001US-0799317 (March 5, 2001), 2000US-207343P (May 30, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200192210 A1	December 6, 2001	E	098	C07C237/20
AU 200165083 A	December 11, 2001		000	C07C237/20
US 20020006957 A1	January 17, 2002		000	A61K031/21

INT-CL (IPC): A61 K 31/17; A61 K 31/18; A61 K 31/21; A61 K 31/26; A61 K 31/325; A61 K 31/34; A61 P 3/10; A61 P 15/10; A61 P 29/00; C07 C 237/20; C07 C 237/22; C07 C 271/18; C07 C 275/24; C07 C 311/04; C07 C 311/17; C07 C 319/00; C07 C 321/00; C07 C 323/00; C07 C 381/00; C07 D 307/42

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Clip Img | Image

☐ 79. Document ID: WO 200105422 A2 EP 1203239 A2 FR 2797402 A1 AU 200065768 A

L5: Entry 79 of 82 File: DWPI Jan 25, 2001

DERWENT-ACC-NO: 2001-159475
DERWENT-WEEK: 200238
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TITLE: Detecting, preventing and treating degenerative, neurological and autoimmune diseases, particularly multiple sclerosis, using specified polypeptides or related nucleic acid or ligand

INVENTOR: CHARLES, M; KOLBE, H ; MALCUS, C ; PERRON, H ; ROECKLIN, D ; SANTORO, L ; CHARLES, M H

PRIORITY-DATA: 1999FR-0009372 (July 15, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200105422 A2	January 25, 2001	F	208	A61K038/17
EP 1203239 A2	May 8, 2002	F	000	G01N033/68
FR 2797402 A1	February 16, 2001		000	A61K038/17
AU 200065768 A	February 5, 2001		000	A61K038/17

INT-CL (IPC): A61 K 31/437; A61 K 38/17; A61 K 48/00; A61 P 25/00; A61 P 25/28; A61 P 37/00; C07 K 14/47; C12 N 15/12; C12 Q 1/68; G01 N 33/53; G01 N 33/564; G01 N 33/68

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 80. Document ID: JP 2000316599 A

L5: Entry 80 of 82 File: DWPI Nov 21, 2000

DERWENT-ACC-NO: 2001-204982
DERWENT-WEEK: 200121
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TITLE: Measuring the activity of calgranulin B on an enzyme, comprises using a myosin substrate, zinc, calcium, ATP and the enzyme of interest, and measuring the level of phosphorylation

PRIORITY-DATA: 1999JP-0128922 (May 10, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2000316599 A	November 21, 2000		007	C12Q001/48

INT-CL (IPC): C12 N 9/12; C12 Q 1/48

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 81. Document ID: WO 200018970 A1 EP 1118681 A9 EP 1118681 A1 JP 2000572417 X

L5: Entry 81 of 82 File: DWPI Apr 6, 2000

DERWENT-ACC-NO: 2000-293189
DERWENT-WEEK: 200244
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TITLE: Controlling the release of granules from cell system using activated calgranulin for screening substances for granule activating or inhibiting activity

INVENTOR: FUKUDA, K; SETO, M

PRIORITY-DATA: 1998JP-0274574 (September 29, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200018970 A1	April 6, 2000	J	042	C12Q003/00
EP 1118681 A9	June 5, 2002	E	000	C12Q003/00
EP 1118681 A1	July 25, 2001	E	000	C12Q003/00
JP 2000572417 X	December 18, 2001		000	C12Q003/00

INT-CL (IPC): C07 K 14/47; C12 Q 1/02; C12 Q 3/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 82. Document ID: EP 263072 A US 5702920 A NO 8704159 A ZA 8707417 A FI 8704287 A AU 8779309 A DK 8705177 A JP 63157997 A PT 85849 A NO 9201024 A EP 263072 B1 DE 3789413 G ES 2052602 T3 US 5350687 A JP 09188698 A

L5: Entry 82 of 82 File: DWPI Apr 6, 1988

DERWENT-ACC-NO: 1988-093533
DERWENT-WEEK: 199807

TITLE: Human macrophage migration inhibition factor related peptide - having immune regulating properties for therapeutic use and used for prodn. of antibodies

INVENTOR: BRUEGGEN, J; CERLETTI, N ; CLERC, R ; ODINK, K ; SORG, C ; TARCSAY, L ; WIESENDANGER, W ; BRUGGEN, J ; ODINK, K G ; WIESENDANG, W

PRIORITY-DATA: 1986GB-0028358 (November 27, 1986), 1986GB-0023850 (October 3, 1986)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 263072 A	April 6, 1988	E	072	
US 5702920 A	December 30, 1997		062	C07K014/52
NO 8704159 A	May 2, 1988		000	
ZA 8707417 A	April 5, 1988		000	
FI 8704287 A	April 4, 1988		000	
AU 8779309 A	May 19, 1988		000	
DK 8705177 A	April 4, 1988		000	
JP 63157997 A	June 30, 1988		000	
PT 85849 A	November 30, 1988		000	
NO 9201024 A	April 5, 1988		000	C12N015/00
EP 263072 B1	March 23, 1994	E	117	C12P021/02
DE 3789413 G	April 28, 1994		000	C12P021/02
ES 2052602 T3	July 16, 1994		000	C12P021/02
US 5350687 A	September 27, 1994		051	C07K005/00
JP 09188698 A	July 22, 1997		065	C07K014/52

INT-CL (IPC): A61K 37/02; A61K 38/00; A61K 39/39; A61K 39/395; C07G 17/00; C07H 21/04; C07K 3/20; C07K 5/00; C07K 7/10; C07K 13/00; C07K 14/52; C07K 15/00; C07K 15/28; C07K 16/24; C12N 1/16; C12N 1/19; C12N 1/20; C12N 1/21; C12N 5/00; C12N 5/10; C12N 5/12; C12N 15/00; C12N 15/09; C12N 15/19; C12N 21/00; C12P 19/34; C12P 21/00; C12P 21/02; C12P 21/08; G01N 33/50; G01N 33/53; G01N 33/54; G01N 33/577; G01N 33/68; C12P 21/00; C12R 1/91 ; C12P 21/02; C12R 1/19; C12P 21/02; C12R 1/91; C12P 21/02; C12R 1/865

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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Term	Documents
CALGRANULIN.DWPI,TDBD,EPAB,USPT,PGPB.	40
CALGRANULINS.DWPI,TDBD,EPAB,USPT,PGPB.	5
MRP-8.DWPI,TDBD,EPAB,USPT,PGPB.	52
MRP-8S	0
MRP-14.DWPI,TDBD,EPAB,USPT,PGPB.	13
MRP-14S	0
(CALGRANULIN OR MRP-14 OR MRP-8).USPT,PGPB,EPAB,DWPI,TDBD.	82
((CALGRANULIN OR MRP-8 OR MRP-14)).USPT,PGPB,EPAB,DWPI,TDBD.	82

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1: Eur J Biochem 1996 Oct 1;241(1):265-71 Related Articles, Links

Phosphorylation of myeloid-related proteins MRP-14 and MRP-8 during human neutrophil activation.

Guignard F, Mauel J, Markert M.

Central Laboratory of Clinical Chemistry, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

The myeloid-related proteins MRP-14 and MRP-8 and also p6, three calcium-binding proteins of the S100 family, translocate to the membrane during human neutrophil activation with stimuli known to require extracellular calcium for activity. When phorbol 12-myristate 13-acetate (PMA, an extracellular calcium-independent stimulus) is used, no translocation is observed. To characterize further the mechanisms involved in their translocation, phosphorylation of these proteins was studied. Three isoforms of MRP-14 were markedly phosphorylated in the membrane and in the cytosol upon activation with extracellular calcium-dependent stimuli, such as opsonized zymosan, the calcium ionophore A23187, N-formylmethionylleucylphenylalanine in the presence of cytochalasin B and arachidonic acid, or upon extracellular calcium-independent stimulation (PMA). In no case were p6 and a fourth, more basic isoform of MRP-14, phosphorylated. In PMA-activated cells, a phosphorylated acidic isoform of MRP-8 was detected in the cytosol only. However, phosphorylated MRP-8 represented only a small fraction of total MRP-8. Cgp 41251, an inhibitor of protein kinase C (PKC), completely inhibited the phosphorylation of MRP-8, and decreased cytosolic MRP-14 phosphorylation. To test whether phosphorylated MRP-8 could translocate, A23187, which induces translocation of the three S100 proteins, was added after PMA activation. This resulted in translocation of 18% +/- 5% of phosphorylated MRP-14 and 19% +/- 1% of only nonphosphorylated MRP-8. However, upon inhibition of PKC, translocation of MRP-14 and MRP-8 was increased up to 38% +/- 7% and 34% +/- 3% respectively. This suggests a putative role of phosphorylation and/or of PKC in the modulation of MRP-14 and MRP-8 translocation to the membrane.

PMID: 8898915 [PubMed - indexed for MEDLINE]

1: J Leukoc Biol 1993 Feb;53(2):197-204 Related Articles, Links

MRP-8 and MRP-14, two abundant Ca(2+)-binding proteins of neutrophils and monocytes.

Hessian PA, Edgeworth J, Hogg N.

Macrophage Laboratory, Imperial Cancer Research Fund, London, United Kingdom.

Two calcium-binding proteins, named migration inhibitory factor-related proteins-8 (MRP-8) and MRP-14, are primarily expressed by circulating human neutrophils and monocytes. Evidence accumulating from the investigations of several independent groups is now leading to an improved understanding of the biology of these proteins. Both MRP-8 and MRP-14 display features characteristic of members of the S100 family of calcium-binding proteins. Some of these features predict functions for MRP-8 and MRP-14 but to date an exact and well-defined function remains elusive. Here we review the available information and highlight evidence that suggests the function of MRP-8 and MRP-14 may be associated with both monocyte and neutrophil activation and the accumulation of these cells in inflammatory sites.

Publication Types:
- Review
- Review, Tutorial

PMID: 8445331 [PubMed - indexed for MEDLINE]

1: J Biol Chem 1991 Jul 15;266(20):13462-7 Related Articles, Links

Calcium-dependent complex assembly of the myeloic differentiation proteins MRP-8 and MRP-14.

Teigelkamp S, Bhardwaj RS, Roth J, Meinardus-Hager G, Karas M, Sorg C.

Institute of Experimental Dermatology, University of Munster, Germany.

MRP-8 and MRP-14 are calcium-binding proteins belonging to the S-100 protein family which have been shown to be associated with specific stages of myeloic/monocytic cell differentiation. Members of this protein family are shown to form homo- and heterodimers. Complex formation has also been observed in preliminary experiments for MRP-8 and MRP-14. To evaluate the in vivo relevance of the MRP complex formation and the stoichiometric ratio of individual components complexes were isolated from granulocytes and monocytes by immunoaffinity chromatography using monospecific antibodies. The purified fraction of the MRPs was found to contain monomers and dimers as shown on sodium dodecyl sulfate-polyacrylamide gel electrophoresis by silver staining and immunoblotting. Similar results were obtained by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and immunoblotting of crude cell extracts. The existence of the MRP complexes in vivo was demonstrated by chemical cross-linking and subsequent isolation of complexes by immunoaffinity chromatography. Two new, highly abundant complexes were found in addition to the heterodimer, but neither monomers nor homodimers were detected. The two larger protein complexes (35.0 and 48.5 kDa) were identified as [MRP-8)2.(MRP-14] trimer and [MRP-8)2.(MRP-14)2) tetramer, respectively. All complexes could be shown to be noncovalently associated in vivo. Furthermore, the association of MRPs was shown to be Ca2+ dependent.

PMID: 2071612 [PubMed - indexed for MEDLINE]

1: J Leukoc Biol 1998 Aug;64(2):214-20

Related Articles, Links

Antinociceptive effect of the calcium-binding protein MRP-14 and the role played by neutrophils on the control of inflammatory pain.

Giorgi R, Pagano RL, Dias MA, Aguiar-Passeti T, Sorg C, Mariano M.

Laboratory of Pathophysiology, Butantan Institute, Sao Paulo, Brazil.

Macrophages secrete a variety of chemical mediators that play a central role in the pathophysiology of inflammatory pain. Therefore, the activation or deactivation of these cells in an inflammatory focus could modulate the intensity of the algogenic response. Based on these premises and on our previous demonstration that the calcium-binding protein MRP-14, highly expressed in neutrophils, deactivates activated macrophages in vitro, we decided to investigate the role of MRP-14 and of neutrophils in the control of inflammatory pain in mice. Our results show that this protein is endowed with antinociceptive activity. When tested in the writhing model it was able to inhibit pain response but did not change the behavior of the animals in the hot plate test. This observation indicates that MRP-14 down-regulates inflammatory but not central pain. Using a model of acute neutrophilic peritonitis induced by glycogen, a close correlation between neutrophil migration and antinociception was detected. Surgical adrenalectomy demonstrated that the antinociceptive response induced by glycogen was not due to endogenous liberation of glucocorticoids. The treatment of animals either with a monoclonal antibody anti-MRP-14 or a monoclonal antibody that depletes the animals of neutrophils reverts the antinociceptive response observed in the glycogen-induced peritonitis. These data define the calcium-binding protein MRP-14 as a novel mediator for the control of inflammatory pain and consequently discloses an anti-inflammatory role for the neutrophil.

PMID: 9715261 [PubMed - indexed for MEDLINE]

1: J Pathol 2000 Dec;192(4):540-4

Related Articles, Links

Identification of MRP-8 (calgranulin A) as a major responsive protein in chronic periodontitis.

Lundy FT, Chalk R, Lamey PJ, Shaw C, Linden GJ.

School of Dentistry, The Queen's University of Belfast, Belfast, UK.

The purpose of the study was to analyse how the protein composition of the inflammatory exudate associated with chronic periodontitis differed from the exudate in periodontal health. Gingival crevicular fluid (GCF) was collected from sites with chronic periodontal inflammation and from non-diseased sites in healthy control subjects. Microbore HPLC analysis revealed one major difference in GCF protein profiles between healthy controls and periodontitis patients. The protein enhanced in periodontitis patients was identified as migration inhibitory factor-related protein-8 (MRP-8) by a combination of N-terminal amino acid sequencing, mass spectrometry, and SDS-PAGE. Together, these data demonstrate, for the first time, the presence of monomeric MRP-8 in an inflammatory exudate. Whether monomeric MRP-8 is a unique feature of chronic periodontal inflammation is not yet clear, but the chemotactic properties of this peptide support a functional role for MRP-8 in periodontal inflammation. Copyright 2000 John Wiley & Sons, Ltd.

PMID: 11113873 [PubMed - indexed for MEDLINE]

1: Biochem J 1995 Jul 15;309 (Pt 2):395-401

Related Articles, Links

Identification and characterization of a novel human neutrophil protein related to the S100 family.

Guignard F, Mauel J, Markert M.

Central Laboratory of Clinical Chemistry, CHUV, Lausanne, Switzerland.

A rabbit polyclonal antibody raised against myeloid-related protein 8 (MRP-8), a protein of the S100 family, recognized another S100 protein (MRP-14) as well as a protein of 6.5 kDa (p6) in the cytosol of resting neutrophils. p6 was found to be a novel member of the S100 family. It consisted of two isoforms with pI values of 6.2 (the minor form, p6a) and 6.3 (the major form, p6b) and constituted 5% of the total cytosolic proteins. Both isoforms were also demonstrated in the cytosol of monocytes, but not in lymphocytes, as previously shown for MRP-8 and MRP-14. Only the major isoform bound radioactive Ca2+, as also observed for MRP-8, whereas the different variants of MRP-14 were all labelled. On neutrophil activation with opsonized zymosan, a stimulant known to require extracellular Ca2+, 58% of p6a and 42% of p6b was translocated to the membrane. With phorbol 12-myristate 13-acetate, a Ca(2+)-independent stimulant, no translocation was detected. This translocation pattern was similar to that observed with MRP-8 and MRP-14. In addition, p6, MRP-8 and MRP-14 were specifically associated with the cytoskeletal fraction of the membrane. The Ca(2+)-dependent translocation of the novel S100 protein in parallel with MRP-8 and MRP-14 suggests a role for these proteins in regulating the Ca2+ signal to the membrane cytoskeleton and thus in regulating neutrophil activation.

PMID: 7626002 [PubMed - indexed for MEDLINE]

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MRP-8 and MRP-14, two abundant Ca(2+)-binding proteins of neutrophils and monocytes.

Hessian PA, Edgeworth J, Hogg N.

Macrophage Laboratory, Imperial Cancer Research Fund, London, United Kingdom.

Two calcium-binding proteins, named migration inhibitory factor-related proteins-8 (MRP-8) and MRP-14, are primarily expressed by circulating human neutrophils and monocytes. Evidence accumulating from the investigations of several independent groups is now leading to an improved understanding of the biology of these proteins. Both MRP-8 and MRP-14 display features characteristic of members of the S100 family of calcium-binding proteins. Some of these features predict functions for MRP-8 and MRP-14 but to date an exact and well-defined function remains elusive. Here we review the available information and highlight evidence that suggests the function of MRP-8 and MRP-14 may be associated with both monocyte and neutrophil activation and the accumulation of these cells in inflammatory sites.

Publication Types:
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PMID: 8445331 [PubMed - indexed for MEDLINE]

1: Eur J Biochem 1996 Oct 1;241(1):265-71 Related Articles, Links

Phosphorylation of myeloid-related proteins MRP-14 and MRP-8 during human neutrophil activation.

Guignard F, Mauel J, Markert M.

Central Laboratory of Clinical Chemistry, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

The myeloid-related proteins MRP-14 and MRP-8 and also p6, three calcium-binding proteins of the S100 family, translocate to the membrane during human neutrophil activation with stimuli known to require extracellular calcium for activity. When phorbol 12-myristate 13-acetate (PMA, an extracellular calcium-independent stimulus) is used, no translocation is observed. To characterize further the mechanisms involved in their translocation, phosphorylation of these proteins was studied. Three isoforms of MRP-14 were markedly phosphorylated in the membrane and in the cytosol upon activation with extracellular calcium-dependent stimuli, such as opsonized zymosan, the calcium ionophore A23187, N-formylmethionylleucylphenylalanine in the presence of cytochalasin B and arachidonic acid, or upon extracellular calcium-independent stimulation (PMA). In no case were p6 and a fourth, more basic isoform of MRP-14, phosphorylated. In PMA-activated cells, a phosphorylated acidic isoform of MRP-8 was detected in the cytosol only. However, phosphorylated MRP-8 represented only a small fraction of total MRP-8. Cgp 41251, an inhibitor of protein kinase C (PKC), completely inhibited the phosphorylation of MRP-8, and decreased cytosolic MRP-14 phosphorylation. To test whether phosphorylated MRP-8 could translocate, A23187, which induces translocation of the three S100 proteins, was added after PMA activation. This resulted in translocation of 18% +/- 5% of phosphorylated MRP-14 and 19% +/- 1% of only nonphosphorylated MRP-8. However, upon inhibition of PKC, translocation of MRP-14 and MRP-8 was increased up to 38% +/- 7% and 34% +/- 3% respectively. This suggests a putative role of phosphorylation and/or of PKC in the modulation of MRP-14 and MRP-8 translocation to the membrane.

PMID: 8898915 [PubMed - indexed for MEDLINE]

1: Hessian PA, Fisher L. Related Articles, Links

The heterodimeric complex of MRP-8 (S100A8) and MRP-14 (S100A9). Antibody recognition, epitope definition and the implications for structure.
Eur J Biochem. 2001 Jan;268(2):353-63.
PMID: 11168370 [PubMed - indexed for MEDLINE]

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The S100 family heterodimer, MRP-8/14, binds with high affinity to heparin and heparan sulfate glycosaminoglycans on endothelial cells.
J Biol Chem. 2002 Feb 1;277(5):3658-65.
PMID: 11723110 [PubMed - indexed for MEDLINE]

3: Propper C, Huang X, Roth J, Sorg C, Nacken W. Related Articles, Links

Analysis of the MRP8-MRP14 protein-protein interaction by the two-hybrid system suggests a prominent role of the C-terminal domain of S100 proteins in dimer formation.
J Biol Chem. 1999 Jan 1;274(1):183-8.
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4: Guignard F, Mauel J, Markert M. Related Articles, Links

The monoclonal antibody Mac 387 recognizes three S100 proteins in human neutrophils.
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Location of a protease-hypersensitive region in the multidrug resistance protein (MRP) by mapping of the epitope of MRP-specific monoclonal antibody QCRL-1.
Cancer Res. 1996 Jul 15;56(14):3307-14.
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Identification and characterization of a novel human neutrophil protein related to the S100 family.
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The three-dimensional structure of human S100A12.

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The dimerization interface of the metastasis-associated protein S100A4 (Mts1): in vivo and in vitro studies.
J Biol Chem. 2001 Jun 29;276(26):24212-22.
PMID: 11278510 [PubMed - indexed for MEDLINE]

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A comparison of human S100A12 with MRP-14 (S100A9).
Biochem Biophys Res Commun. 2000 Sep 7;275(3):865-70.
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Epitope identification for human neutrophil flavocytochrome b monoclonals 48 and 449.
Eur J Haematol. 2000 Dec;65(6):407-13.
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Characterization of a B cell surface antigen with homology to the S100 protein MRP8.
Biochem Biophys Res Commun. 1999 Sep 16;263(1):17-22.
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Human pancreatic lipase: an exposed hydrophobic loop from the C-terminal domain may contribute to interfacial binding.
Biochemistry. 1998 Aug 25;37(34):11846-55.
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☐ 16: Hessian PA, Edgeworth J, Hogg N. Related Articles, Links
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J Leukoc Biol. 1993 Feb;53(2):197-204. Review.
PMID: 8445331 [PubMed - indexed for MEDLINE]

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Novel insights into structure and function of MRP8 (S100A8) and MRP14 (S100A9).
Biochim Biophys Acta. 1998 Dec 10;1448(2):200-11. Review.
PMID: 9920411 [PubMed - indexed for MEDLINE]

☐ 18: Deloulme JC, Assard N, Mbele GO, Mangin C, Kuwano R, Baudier J. Related Articles, Links

S100A6 and S100A11 are specific targets of the calcium- and zinc-binding S100B protein in vivo.
J Biol Chem. 2000 Nov 10;275(45):35302-10.
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☐ 19: Ramanathan L, Ingram R, Sullivan L, Greenberg R, Reim R, Trotta PP, Le HV. Related Articles, Links
Immunochemical mapping of domains in human interleukin 4 recognized by neutralizing monoclonal antibodies.
Biochemistry. 1993 Apr 13;32(14):3549-56.
PMID: 7682108 [PubMed - indexed for MEDLINE]

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Structural basis of the Ca(2+)-dependent association between S100C (S100A11) and its target, the N-terminal part of annexin I.
Structure Fold Des. 2000 Feb 15;8(2):175-84.
PMID: 10673436 [PubMed - indexed for MEDLINE]

1: Parasitology 1996 Oct;113 (Pt 4):403-14

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Neutrophil granule proteins: evidence for the participation in the host reaction to skin microfilariae of Onchocerca volvulus after diethylcarbamazine administration.

Gutierrez-Pena EJ, Knab J, Buttner DW.

Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany.

The participation of neutrophil granulocytes in the cellular reaction to skin microfilariae of Onchocerca volvulus was studied by immunohistochemistry. Skin biopsies were obtained from adult Liberian and Ugandan patients with generalized onchocerciasis after exposure to topically applied diethylcarbamazine (DEC) and from untreated patients. After DEC many damaged microfilariae were observed either in dermal infiltrates or in epidermal microabscesses consisting both of neutrophils and eosinophils. Infiltrates and microabscesses contained some intact granulocytes and many neutrophils releasing myeloperoxidase, elastase, lactoferrin, defensin, lysozyme, alpha 1-antitrypsin and alpha 1-antichymotrypsin. Eosinophils discharged peroxidase and cationic proteins. Released granule proteins and remnants of disrupted granulocytes were found on the surface and in close proximity of damaged microfilariae in dermal infiltrates and epidermal microabscesses. In larger microabscesses neutrophils were predominant. These observations show that neutrophils and not only eosinophils recruit, accumulate, localize around and release their helminthotoxic granule proteins such as myeloperoxidase onto or closely around skin microfilariae of O. volvulus after topical DEC administration. The association between these processes and the damage of the microfilariae indicated that neutrophils together with eosinophils attack and damage microfilariae of O. volvulus after DEC treatment in the skin.

PMID: 8873478 [PubMed - indexed for MEDLINE]

Application Number Information

Application Number: **09/806382** **Assignments**
Filing Date: **03/29/2001**
Effective Date: **03/29/2001**
Application Received: **03/29/2001**
Patent Number:
Issue Date: **00/00/0000**
Date of Abandonment: **00/00/0000**
Attorney Docket Number: **ASAHI-3-PC-1**
Status: **71 /RESPONSE TO NON-FINAL OFFICE ACTION ENTERED AND FORWARDED TO EXAMINER**
Confirmation Number: **6829**
Title of Invention: **METHOD FOR CONTROLLING THE RELEASE OF GRANULES**

Examiner Number: **79120 / LIU, SAMUEL**
Group Art Unit: **1653**
Class/Subclass: **514/012.000**
Lost Case: **NO**
Interference Number:
Unmatched Petition: **NO**
L&R Code: Secrecy Code:**1**
Third Level Review: **NO**
Secrecy Order: **NO**
Status Date: **09/05/2002**

Bar Code	Location	Location Date	Chrg to Loc	Charge to Name	Emp. ID	Infra Loc
09806382	**16L2 TC 1600 LEGAL INSTRUMENTS EXAMINER TEAM 2, CM1-9C10**	**09/05/2002**	**16X1**	**LIU, SAMUEL**	**DWILLIAMS2**	**CM1/09/C 10**

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1: J Biol Chem 1992 Sep 25;267(27):19379-82 Related Articles, Links

Translocation of a small cytosolic calcium-binding protein (MRP-8) to plasma membrane correlates with human neutrophil activation.

Lemarchand P, Vaglio M, Mauel J, Markert M.

Central Laboratory of Clinical Chemistry, CHUV, Lausanne, Switzerland.

To further understand the mechanisms involved in phagocyte activation in general and in NADPH oxidase activation in particular, a polyclonal antibody was raised in rabbit against a partially purified oxidase preparation. The enzyme was solubilized from zymosan-activated human neutrophils and resting cells and separated by preparative isoelectric focusing electrophoresis. A polyclonal antibody was raised in rabbit against the pI 5.0 fraction, which had the maximum superoxide-producing capacity. Analysis of the polyclonal antibody revealed marked differences between activated and resting neutrophils. The antibody recognized in particular an 8-kDa protein (p8) in resting human neutrophil cytosol and in the membrane of zymosan-activated cells. A polyclonal antibody (anti-p8) was raised against the pure cytosolic p8 protein. This anti-p8 reacted not only with p8, but also with cytosolic proteins of 14 kDa and 6 kDa. N-terminal amino acid sequence analysis of p8 revealed homology with the calcium-binding myeloid related protein (MRP-8). Upon neutrophil activation, translocation of the 8- and 14-kDa proteins to the membrane was observed with stimuli known to depend on extracellular calcium. In calcium-depleted medium, the absence of translocation correlated with a depression of superoxide production, supporting a role for the calcium-binding protein in cellular activation.

PMID: 1326551 [PubMed - indexed for MEDLINE]

☐ 1: AIDS 2001 Mar 9;15(4):441-9

Related Articles, Links

Myeloid-related protein (MRP)-8 from cervico-vaginal secretions activates HIV replication.

Hashemi FB, Mollenhauer J, Madsen LD, Sha BE, Nacken W, Moyer MB, Sorg C, Spear GT.

Department of Immunology/Microbiology, Section of Infectious Diseases, Rush Medical College, Chicago, Illinois 60612, USA.

OBJECTIVES: To identify a substance found in female genital tract secretions that enhances HIV expression in infected cells. DESIGN: Cervico-vaginal lavages (CVL), collected in sterile normal saline, were fractionated and tested for HIV-inducing activity using HIV-infected monocytes. METHODS: To purify the component(s) of CVL that enhance HIV production, Mono-Q ion exchange chromatography followed by Superose-12 molecular sieve analysis, and SDS--PAGE were performed. The purified protein was identified by amino acid sequence analysis. RESULTS: SDS--PAGE of bioactive fractions showed a 14 kDa polypeptide band. Amino acid sequence analysis of selected peptides from the 14 kDa band showed 100% homology with the myeloid-related protein (MRP)-8, an inflammatory protein found in mucosal secretions. Western blot analysis revealed that bioactive CVL contained more immunoreactive MRP-8 than samples without bioactivity. The HIV-inducing activity of MRP-8 was further confirmed by showing that human recombinant MRP-8 increased HIV expression by up to 40-fold. CONCLUSIONS: MRP-8 in cervico-vaginal secretions stimulates HIV production. Strategies aimed at blocking MRP-8 activity in the genital tract could reduce risk of sexual as well as maternal--infant transmission of HIV.

PMID: 11242140 [PubMed - indexed for MEDLINE]